

AJDC

AMERICAN JOURNAL OF DISEASES OF CHILDREN

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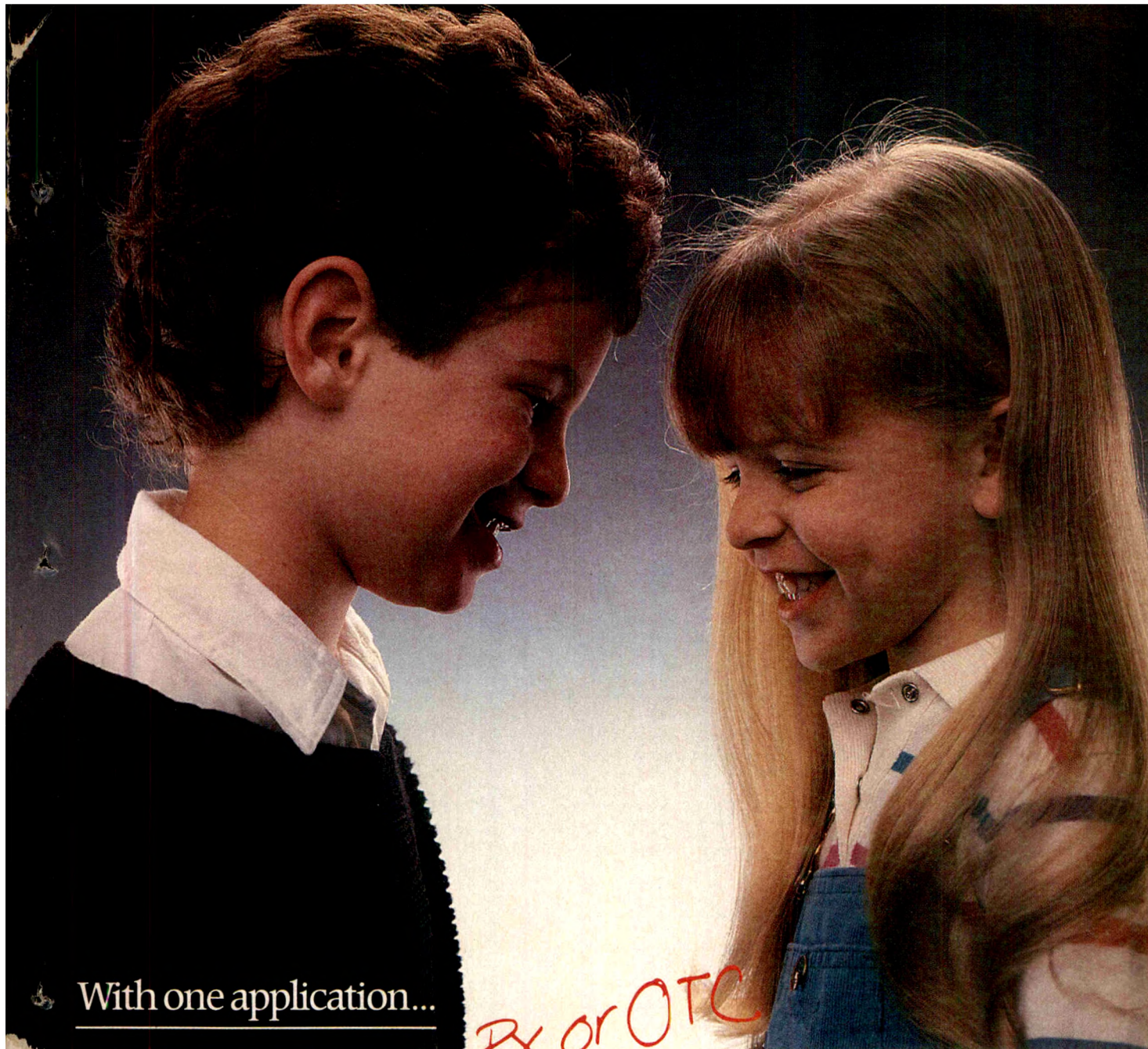
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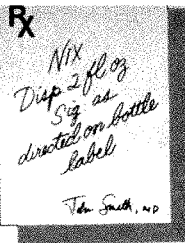


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WARNING: If hypersensitivity to Nix occurs, discontinue use.

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Pregnancy: Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits (200-400 mg/kg/day orally) and have revealed no evidence of impaired fertility or harm to the fetus due to permethrin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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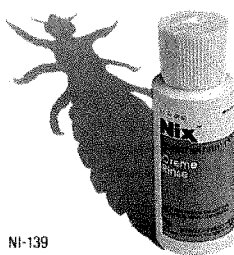
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References:

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On Jan 1, 1988, *AJDC* initiated a new procedure. Manuscripts submitted to *AJDC* will NO LONGER BE RETURNED, except in the case of accepted manuscripts or those undergoing author revision. Original artwork and photographs will be returned.

General Information.—Please send manuscripts and correspondence by first-class mail (do not use registered, certified, or express mail) to the Editor, Vincent A. Fulginiti, MD, *AJDC*, Dean's Office, Room 1529, Tulane University, School of Medicine, 1430 Tulane Avenue, New Orleans, LA 70112. All accepted manuscripts are subject to copy editing. The corresponding author will receive an edited typescript and layout for approval. Forms for ordering reprints are included with the edited typescript. Reprints are shipped six to eight weeks after publication. Proofs will be sent for approval if requested by the author and if printing deadlines permit. The author is responsible for all statements in his/her work, including changes made by the copy editor.

Conforming with all of the steps listed below will facilitate the editorial processing of your manuscript.

Step 1.—Cover Letter.—All manuscripts must be accompanied on submission by a cover letter giving the name, address, affiliation, and telephone number of the corresponding author. The letter must include ALL of the following statements SIGNED BY ALL AUTHORS (ORIGINAL SIGNATURES):

1. **Copyright Release.**—"In consideration of the American Medical Association's taking action in reviewing and editing this submission, the author(s) undersigned hereby transfer(s), assign(s), or otherwise convey(s) all copyright ownership to the AMA in the event that this work is published by the AMA."

2. **Statement of Affirmation.**—"This manuscript has not been published anywhere in any language and is not under simultaneous consideration by another publication. This manuscript is original and ALL authors have seen and approve of its contents."

3. **Financial Disclosure.**—List all affiliations with or financial involvement in organizations or entities with a direct financial interest in the subject matter or material of the research discussed in the manuscript (eg, employment consultancies, stock ownership) OR include a statement disclaiming any such involvement. All such information will be held in confidence during the review process. Should the manuscript be accepted, the Editor will discuss with the author the extent of disclosures appropriate for publication. All accepted manuscripts become the permanent property of the publisher (AMA) and may not be published elsewhere without written permission from the AMA. After publication certain articles may appear in translation in the foreign-language edition(s) of *AJDC*.

Step 2.—Manuscript Format.—All articles submitted should have the following features:

1. Four copies of the manuscript should be submitted; three are for transmission to referees and one is to be retained in the editorial office. We prefer an original and three copies.

2. Manuscripts should be typed in triple-spaced format on heavy-duty white bond paper, 21.6×27.9 cm (8½×11 in) with 2.5-cm (1-in) margins. Do not use justified right margins.

3. Title should be no more than 75 characters.

4. Authors should be limited to six, all of whom have contributed to the study and manuscript preparation, are familiar with its substance, and are able to defend its conclusions.

5. The title page should give full names, degrees, and academic affiliations of all authors, address for request of reprints, and, if the manuscript was presented at a meeting, the organization, place, and exact date on which it was read.

6. Writing style should conform to proper English usage and syntax; consult the *American Medical Association Manual of Style*, available from Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202.

7. Abstract should be limited to 135 words or less.

8. Each table should be typed, with a title, on a separate sheet of paper, with each line, including headings, double-spaced. Continuations should be on a second sheet with all headings repeated.

9. Use Systeme International (SI) measurements throughout the manuscript.

10. Illustrations should be high-contrast, glossy prints, in quadruplicate, unmounted and untrimmed; lettering should be legible after reduction to column size. Figure number, name of first author, and arrow indicating "top" should be typed on a gummed label and affixed on the back of each illustration. Do not write directly on the print.

Magnification and stain should be provided for histologic sections. Full-color illustrations should be submitted as 35-mm, positive color transpa-

encies, mounted in cardboard and carefully packaged. Do not submit glass-mounted transparencies or color prints. Fee is \$400 for up to six square-finished color illustrations that fit on one page. A letter of intent to pay the fee must accompany submission.

All photographs in which there is a possibility of patient identification should be accompanied by a signed statement of consent from both parents (or guardians). Covering eyes to mask identity is not sufficient.

11. References should be listed in order of their appearance in the text, type double-spaced, and in AMA format. Please follow the exact order of information and punctuation in the examples below.

Journal Articles: Sell EJ, Gaines JA, Gluckman C, Williams E. Persistent fetal circulation: neurodevelopment outcome. *AJDC*. 1985;139:25-28.

Books: Krmpotic-Nemanic J, Kostovis I, Rudan P. Aging changes of the form and infrastructure of the external nose and its importance in rhinoplasty. In: Conly J, Dickinson JT, eds. *Plastic and Reconstructive Surgery of the Face and Neck*. New York, NY: Grune & Stratton; 1972:84-91.

Unpublished data, personal communications, or manuscripts "in preparation" or "submitted" should not be included in the list of references. Such material, if essential, may be incorporated in the body of the article.

Authors are responsible for the accuracy of the references.

12. Investigations involving human subjects require a specific statement in the "Methods" section that an appropriate institutional review board approved the project and/or that informed consent was obtained from both legal guardians and/or child, if appropriate.

13. Illustrations and tables from other publications should be suitably acknowledged, with written permission from publisher and author. Brief acknowledgements to specific contributors directly involved in the content of the manuscript may be placed at the end of the text, before the references. General acknowledgements will be deleted.

Step 3.—Special Departments.—Criteria for several special departments are given below.

1. **The Pediatric Forum.**—This is the place for comment, criticism, observations, and discussion of "issues of current concern and importance for children's health," in addition to letters that comment on articles in previous issues of *AJDC*. The Editor reserves the right to conduct review of and to edit all submissions. THE READER SHOULD SUBMIT TRIPLE-SPACED COPY CLEARLY MARKED "FOR PUBLICATION" AND SIGNED BY ALL AUTHORS. REFERENCES, IF INCLUDED, SHOULD CONFORM TO THE USUAL AMA FORMAT. Copyright assignment, signed by all authors, must accompany the original submission.

2. **From Research to Relevance.**—PURPOSE: To focus on significant research that has a high probability of being translated into clinical usefulness.

3. **Educational Interventions.**—PURPOSE: To share information concerning any educational efforts in the broad field of pediatrics.

4. **Sports Medicine.**—PURPOSE: To provide current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention, diagnosis, and treatment of sports-related illnesses and injuries.

5. **Picture of the Month.**—Submissions should be sent directly to Murray Feingold, MD, National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135, and should conform to the format for original articles in terms of the text, references, and illustrations.

6. **Radiological Case of the Month.**—Submissions should be sent directly to Beverly P. Wood, MD, University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Submissions should conform to the format for original articles in terms of the text, references, and illustrations.

Author's Checklist

- ____ 1. Cover letter with name, address, and telephone number of corresponding author.
- ____ 2. Copyright transmittal, affirmation, and financial statements signed by ALL authors.
- ____ 3. Original typed manuscript plus three copies.
- ____ 4. Triple-spacing; double-spacing for tables and legends.
- ____ 5. Right margins UNJUSTIFIED.
- ____ 6. Title 75 characters or less.
- ____ 7. Abstract included.
- ____ 8. References in proper format, cited in numerical order.
- ____ 9. Four sets of illustrations.
- ____ 10. Four sets of legends for illustrations.
- ____ 11. Proper consent forms for patient photographs.
- ____ 12. Permission forms for illustrations previously published elsewhere.

The Pediatric Forum

This department of AJDC is reserved for comment, criticism, observation, and discussion of "issues of current concern and importance for children's health." The Editor encourages our readers to express themselves on a variety of topics and issues. Further, we encourage the submission of unique and brief clinical and scientific observations that do not fulfill the criteria for original articles.

The Diagnosis of Group A, β -Hemolytic Streptococcal Pharyngitis in the Office Setting

Sir.—I read with interest the article in the January 1989 issue of *AJDC* by Taubman et al¹ reporting that a latex agglutination test for direct detection of group A streptococci had a sensitivity of 89.4% and a specificity of 85.7%. Several points in the "Results" and "Comment" sections of the report, however, are of concern.

The authors observed that the sensitivity reported by Roddey et al² was significantly lower than that found in their own study, a difference they attributed to "... the difference in the experience of the people performing the latex test." Another very possible explanation is that, in the study by Roddey et al, sheep blood agar cultures were incubated for 36 to 48 hours if negative after 12 to 24 hours, in contrast to the 18 to 24 hours of incubation reported by Taubman et al. Increased recovery of group A streptococci from sheep blood agar cultures incubated for a second day has been reported to range from 5% to 26%.³⁻⁶ The sensitivity as reported in the very thorough study by Roddey et al, therefore, may more truly reflect the product's performance compared with a carefully performed culture in a pediatrician's office.

The specificity of the latex method (85.7%) as reported in the study of Taubman et al is considerably lower than that reported for the same product in most other studies, as reviewed by Facklam.⁷ This indicates the possibility that some of the "false-positive" results obtained by Taubman et al just might, in fact, have been true-positive results in the face of false-negative culture results.

Taubman et al stated that they compared the latex agglutination test performed in the office of pediatricians

with throat cultures performed in the same office. However, the sensitivity and specificity figures that they reported for the product (calculated from data in Table 1 of the report) come from a comparison of latex test results from the physicians' office with culture results obtained after the cultures were sent to their reference laboratory. The comparison of results of the latex test with those from the pediatrician-read office cultures was not given in the report.

The information on performance of group A streptococcal antigen detection products as presented by Taubman et al is helpful and serves as another point of reference. It appears to be premature, however, to recommend completely replacing a competent culture with this kind of antigen assay until improvements in the assay are made by the manufacturer or until another assay with a well-documented improved sensitivity is marketed.

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1. Taubman B, Barroway RP, McGowan KL. The diagnosis of group A, β -hemolytic streptococcal pharyngitis in the office setting. *AJDC*. 1989;143:102-104.

2. Roddey OF, Clegg HW, Clardy LT, Martin ES, Swetenburg RL. Comparison of a latex agglutination test and four culture methods for identification of group A streptococci in a pediatric office laboratory. *J Pediatr*. 1986;108:347-351.

3. Lauer BA, Reller LB, Mirrett S. Effect of atmosphere and duration of incubation on primary isolation of group A streptococci from throat cultures. *J Clin Microbiol*. 1983;17:338-340.

4. Schaub IG, Mazeika I, Lee R, Dunn MT, LaChaine R-A, Price WH. Ecologic studies of rheumatic fever and rheumatic heart disease. I: procedure for isolating β -hemolytic streptococci. *Am J Hygiene*. 1957;67:46-56.

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6. Libertin CR, Wold AD, Washington JA II. Effects of trimethoprim-sulfamethoxazole and incubation atmosphere on isolation of group A streptococci. *J Clin Microbiol*. 1983;18:680-682.

7. Facklam RR. Specificity study of kits for detection of group A streptococci directly from throat swabs. *J Clin Microbiol*. 1987;25:504-508.

In Reply.—A major purpose of our study was to evaluate both latex tests and cultures when both tests were performed by pediatricians. It had been our practice to read culture results the morning after specimens were plated, a maximum of 24 hours. Since a survey we conducted of pediatricians and family practitioners in the Delaware Valley area showed this was also the practice of the vast majority of physicians polled, we did not alter the practice for the study. However, the cultures were incubated for at least an additional 24 hours before they were read by the reference laboratory. The sensitivity of the latex agglutination test we reported of 89.4% was determined using the results of the reference laboratory reading of the cultures. Therefore, the cultures were incubated for the same length of time before reading as the cultures in the study by Roddey et al and this may not be used to explain the difference in the sensitivity of the latex test or the specificity as suggested by Dr Kellogg.

Direct comparison of the latex test with pediatrician-read office cultures was not done since either could be incorrect. To compare the two tests one must see how accurate each is when compared with "the gold standard," which, in this case, was the reference laboratory reading of the cultures. This was, in fact, done in our study (Tables 1 through 3).

We clearly do not advocate replacing throat cultures with a latex assay in all situations. For the practitioners, the decision depends greatly on the

quality of the alternative, which, for most, are office cultures. Given that even when done under the most optimal conditions and care the sensitivity of office cultures is about 90%, we are concerned that in many offices the sensitivity is much lower. When that is the case, the office latex test may be the superior alternative.

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Assessment of Neurodevelopmental Outcome in Surfactant-Replacement Therapy

Sir:—Surfactant-replacement therapy has achieved a position of great prominence recently in the pediatric literature. The article by Vaucher et al¹ in *AJDC* on the neurodevelopmental outcome of infants treated with human surfactant appears, like the surfactant recipients, to be premature. Two major problems are apparent. First, although the two clinical trials of surfactant replacement were carefully designed, the study population was reduced both by deaths and by those "unavailable for follow-up." Although the authors may have examined differences between those patients who returned for follow-up and those who did not, they did not present such information in their article. With the smaller sample sizes, the possibility of type II error increases and the authors' conclusions of "comparable neurologic and developmental outcome during early childhood in human surfactant-treated and control infants" are not thoroughly supported by their data. Type II error involves not rejecting the null hypothesis when it is false.² In other words, if we conclude that a treatment does *not* make a difference when it indeed *does*, we are guilty of type II error. The probability of making a type-II error (β) is a

function of both sample size and the α level chosen as "statistically significant." If, in the study by Vaucher et al,¹ we combine children with mild, moderate, and severe developmental delay, we find an adverse outcome in approximately 60% (11/17) of the controls and 45% (10/22) of the surfactant-treated children. If we assume that a traditional $\alpha = .05$ was used, given the difference observed and the sample size, $\beta > .5$.³ Thus, a 15% difference would be considered not significant. Only with 98 patients in both the control and study groups would a difference of this size have a 50% chance of being recognized as statistically significant. More recently, retrospective sample-size calculations based on risk reduction have been described by Detsky and Sackett.⁴ The advantage of this retrospective sample-size calculation is that knowledge of the frequency of events (eg, neurodevelopmental delay) in the control and study populations often results in more accurate and smaller sample sizes. If we use the charts provided by Detsky and Sackett⁴ for retrospective sample-size calculations, 15 patients are needed in each group to detect even a 25% risk reduction (or risk increase as the case may be). To detect a smaller change in risk, such as 15%, larger sample sizes are needed. Thus, only if children with mild, moderate, and severe developmental delay were combined and only if a minimum 25% change in risk were considered clinically significant would Vaucher and colleagues be able to draw a "true-negative" conclusion.

This brings us to the second problem, that of the different developmental tests used and the time of administration. The authors employed a variety of developmental assessment tools that vary somewhat in the measures employed. The Knobloch-Gesell Developmental Screening Inventory consists of selected items from the Gesell Developmental Schedules and provides ratings of adaptive, gross motor, fine motor, language, and personal-social characteristics.⁵ The Griffiths Mental Developmental Scales equally weigh five similar areas (locomotor, personal-social, hearing and speech, eye and hand, and performance) to derive a total score.⁶ The Bayley Scales of Infant Development provides two scores—a mental score (Mental Developmental Index) and a motor score (Psychomotor Developmental Index).⁶ The authors also men-

tion use of the Stanford-Binet Scale for children 36 to 48 months of age but only one child was tested! It is unclear to me why one developmental test was not uniformly employed for a given age range throughout the population. More disturbing is the fact that the authors have reported "only the single most recent test result for each child." Consequently, the assessment reported may have occurred as early as 6 months' or as late as 24 months' adjusted age. Recent studies^{7,8} have suggested that scores achieved by prematurely born children on some of these tests frequently are not stable over this time period. Over a longer period, children with an early diagnosis of cerebral palsy often experience resolution or lessening of motor impairment.⁹ Developmental processes may help one child to improve and overcome dystonia of prematurity while another child's spastic diplegia may become more pronounced and cause increasing dysfunction over time. Comparison of developmental test results over such a broad age range is at least unscientific. It is thus very difficult to accept the authors' conclusion of comparable neurodevelopmental outcome in surfactant-treated and control populations. Although surfactant-replacement therapy holds promise for increasing survival rates for very premature infants, the study by Vaucher et al does not dispel the possibility that the potentially greater number of survivors may include a larger proportion of severely impaired children.

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1. Vaucher YE, Merritt TA, Hallman M, Jarvenpaa A-L, Telsey A, Jones BL. Neurodevelopmental and respiratory outcome in early childhood after human surfactant treatment. *AJDC*. 1988;142:927-930.

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In Reply.—We appreciate Dr Langkamp's concern that the widespread use of surfactant-replacement therapy among very-low-birth-weight infants with surfactant deficiency might result in an exchange of increased neurodevelopmental morbidity for decreased mortality caused by respiratory distress syndrome. Although a larger patient population would be ideal to exclude a type II error conclusively, our follow-up data, based on a randomized, controlled trial of human surfactant replacement, did not indicate substantial differences in major neurologic or developmental sequelae, such as cerebral palsy or severe mental retardation, between surfactant recipients and placebo-treated infants receiving conventional ventilation. We cannot yet exclude differences between the two groups in later sequelae, such as communication disorder, attention-deficit disorder, perceptual-motor abnormalities, or learning disability. While a 100% follow-up rate is desirable, this is difficult to accomplish in most regions of the United States given family mobility, high frequency of low socioeconomic status, and the lack of universal access to health care. Among Finnish infants, for whom health care services are universally available and centralized regardless of family locale the follow-up rate was nearly 100%, and we were encouraged to find neurodevelopmental outcomes similar to those reported in American infants. As we noted, a longer-term study may reveal differences based on the disparate demographic characteristics of the two patient groups.

Each of the developmental tests employed in our study assesses cognitive and motor function and is standardized for specific age groups within each population. Because different examinations were used, the data were compared in terms of deviation from the test mean rather than as numeric scores. A single assessment was used for each infant to avoid bias resulting from differing numbers of examinations per child. We used the most recent age-adjusted test results for each child to improve the correlation between this early assessment of development with later estimates of intellectual function.¹⁻³ While the age

range of infants tested in our study was broad, the median adjusted age at examination was 24.5 months.

Our study, like previously published ones, does not address the issue of longer-term neurodevelopmental outcome. Indeed, mild neuromotor abnormalities detected during the first year of life are often transient, although they may be markers for later developmental problems at school age, and infants with cerebral palsy identified at 12 to 24 months of age may be neurologically normal in later childhood. Rather, our purpose was to determine whether infants treated with surfactant demonstrated more adverse early neurological or developmental outcome, as was recently reported by Dunn and coworkers in Toronto, Canada.⁴ Our data demonstrate no significant differences in 2-year outcome between surfactant-treated and control groups. A larger and longer-term follow-up study of our diverse patient populations is currently under way to exclude definitively any differences in neurodevelopmental outcome between infants receiving human surfactant and those treated only with traditional ventilatory techniques. Our data support the use of exogenous surfactants as investigational agents in very-low-birth-weight infants. To answer definitively questions regarding long-term efficacy of this approach to respiratory distress syndrome, additional randomized, controlled clinical trials, not case registries, are needed. Clearly, longer-term follow-up studies must be incorporated in the design of ongoing clinical trials of a variety of surfactants.

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We note that in our Table footnote, a decimal point was missing; the SEM should have read 1.5 months, not 15 months.

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4. Dunn MS, Shennan AT, Hoskins EM, Lennox K, Enhorning G. Two-year follow-up of infants enrolled in a randomized trial of surfactant replacement therapy for prevention of neonatal respiratory distress syndrome. *Pediatrics*. 1988; 82:543-547.

Are 'Hot' Ears Really Hot?

Sir.—Recordings from the tympanic membrane appear superior to those obtained from most other sites commonly used for measuring body temperature.¹⁻⁷ Infrared determinations of temperature have been shown to be fast and accurate^{1,2} and have been used to monitor localized increases in temperature from a variety of causes and sites.¹ We used a commercially available device that measures tympanic membrane temperature (FirstTEMP, Intelligent Medical Systems Inc, Carlsbad, Calif) to explore the effect of otitis media on that temperature. We assumed that patients with unilateral otitis media would display a difference in ear temperature measurements that reflected the magnitude of the local effect of the otitis, ie, that the normal ear would reflect the core temperature and the infected ear would reflect the local increase because of the infection.

Patients and Methods.—Unilateral otitis media was defined as an acute illness with a normal ear opposite a red tympanic membrane that was either immobile or bulging. Sixty-two such patients underwent bilateral infrared measurements to compare the normal ear with the infected ear. Uninfected ears had temperature recordings ranging from 36.1°C to 40.3°C with a mean of 37.58°C, while the infected ear temperatures ranged from 36.3°C to 40.3°C with a mean of 37.67°C. Figure 1 displays the plot of temperatures from infected ears on the y axis vs normal ears on the x axis. The correlation between the infected and normal ears was significant and positive ($r = .91$; $r^2 = .83$; $P = .0001$). The regression equation was as follows: infected ear equals 0.903 times the normal ear plus 0.07. The average (\pm SD) difference between the two ears was $0.094^\circ\text{C} \pm 0.38^\circ\text{C}$. Figure 2 shows the frequency distribution of the difference between infected and uninfected ear temperatures.

Comment.—The center for thermoregulation in the hypothalamus responds to its vascular perfusion temperature, presumably directing the changes that generate the events that modify in core temperature.^{3,4} For a patient at a thermic steady state, febrile or otherwise, a number of sites have been used to estimate core temperature. Those sites—cutaneous, axillary, sublingual, rectal, esophageal,

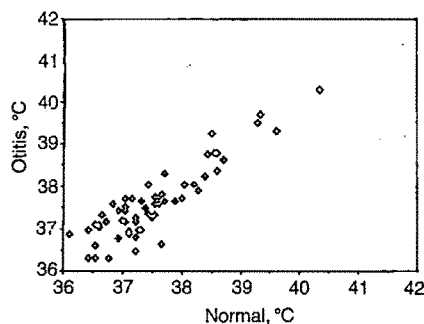


Fig 1.—Scattergram of temperatures of infected vs normal ears.

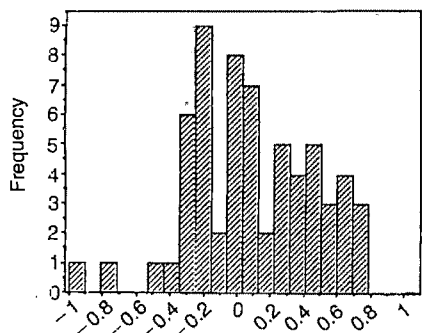


Fig 2.—Frequency distribution of the distribution of the difference between infected and normal ears.

and central venous—have varying levels of patient discomfort and technical difficulty.¹⁻⁶ The technically simpler sites suffer from perfusion difficulties that reduce their response to change and therefore limit usefulness in the thermally unstable patient. Areas such as the tympanic membrane that are well perfused and that share vascular supply with the hypothalamus are ideal for temperature sampling.^{3,6} Initial tympanic temperature recorders were sealed in the canal close to the tympanic membrane, but discomfort and complications limited their use to special cases, ie, anesthetized patients and astronauts.⁷ This problem is solved with measurement of infrared radiation from the tympanic membrane.

Infrared energy radiating differentially from various sources has been used for military "night vision," for night photography, for crop or weather analysis from satellites, and for temperature recording from a distance in scientific studies.¹ Infrared energy radiating from the ear is used clinically to measure body temperature and has been shown to correlate well with other measurements of core temperature.^{1,2} In fact, the technique offers

theoretical and practical advantages over more peripheral measurements. It is obtained quickly and easily and is well tolerated; cross-contamination is less likely; and the response time to temperature change is virtually instantaneous.^{1,2}

Since local heat is a classic sign of infection and since otitis is common in children, we proposed that an ear with unilateral otitis media would yield higher temperature determinations than in the normal ear. Localized infection of one middle ear should not alter perfusion of the contralateral normal ear. The normal ear should reflect the perfusion of the hypothalamic thermoregulatory center. The temperature increase in the infected ear compared with that in the normal ear should then disclose the local thermal effect of the otitis. Using the FirstTEMP device, we found the infected ears to be $0.094^{\circ}\text{C} \pm 0.38^{\circ}\text{C}$ hotter than the uninfected ears, and we propose that the local heat effect of otitis media is of that order. This difference was not large enough to interfere with the clinical use of ear infrared measurements in patients with otitis media as an approximation of core temperature. We conclude that "hot" ears are only approximately 0.1°C hotter than normal, ie, that hot ears are not very hot.

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Cholecystectomy in Sick Cell Anemia

Sir.—In the July 1988 issue of *AJDC*, Malone and Werlin¹ reported the re-

sults of preoperative transfusion before elective cholecystectomy at the time of diagnosis of cholelithiasis in children with sickle cell anemia. Our own practice supports the conclusions of this study.

From 1976 to 1988, 240 children have been seen at the sickle cell clinic. Over the last 10 years, 24 children with sickle cell anemia (mean age, 10.5 years) underwent surgery for cholelithiasis in the Pediatric Surgery Unit at Centre Hospitalier Régional et Universitaire de la Guadeloupe. An annual ultrasonography study detected gallstones in 9 patients.

Fifteen children had a history of recurrent abdominal pain. Of these, 10 were admitted because of acute complications (4 patients with acute cholecystitis, 1 with biliary pancreatitis, and 5 with choledocol stones, with jaundice and cholangitis).

From 1979 to 1985, 13 children underwent surgery without preoperative transfusions. Seven of these children experienced postoperative complications (5 developed pneumonia, 1 developed osteomyelitis, and 1 developed wound sepsis). The preoperative mean hemoglobin level was 76 g/L, with a range of 60 to 100 g/L.

From 1985 to 1988, 11 children received preoperative transfusions and underwent surgery without any postoperative complications. The mean preoperative hemoglobin level was 128 g/L, with a range of 110 to 150 g/L.

The protocol we used is straightforward. If the total hemoglobin level is greater than 85 g/L and less than 120 g/L, the child receives a 10-mL/kg transfusion with packed red blood cells 1 day before surgery. If the total hemoglobin level is less than 85 g/L, a 20-mL/kg transfusion with packed red blood cells is given 2 days before surgery. Before transfusion, one third of the transfused blood is sampled from another vein. If the total hemoglobin level remains less than 120 g/L, an additional 10-mL/kg transfusion of packed red blood cells is given the day before surgery.

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Drug Usage Among Adolescents: A Survey From a Pediatric/ Adolescent Practice

Sir.—Studies have documented alcohol and other drug usage among the adolescent population. In 1985, in a study of over 17 000 high school students, 75% admitted to trying alcohol, 60% marijuana, and 16% cocaine.¹ Because these statistics, along with other statistics from similar studies, involve a cross section of the population, the percentages of drug usage by adolescents in a given practice might be very different. Depending on many factors, including demographics, socioeconomic status, ethnic population served, and geographic areas (urban vs rural), the figures in any pediatric practice may be dissimilar to the figures quoted.

In dealing with the problem of drug usage/abuse in an adolescent population in one's own practice, it might be beneficial to know what the statistics are in regard to drug usage in the population being served. In the process of obtaining information about the deliberate intoxication of children and pets by adolescents, I obtained general information concerning drug usage.² The study population consisted of an upper-middle-class population in a suburb of San Diego, Calif.

Subjects and Methods.—My practice is that of a pediatrician in a large multispecialty group who has had fellowship training in adolescent medicine. The statistics are from a survey that was conducted between March and June of 1987. The group practice serves as a health maintenance organization as well as a private practice setting.

One hundred three male adolescents and 100 female adolescents between the ages of 12 and 18 years completed an anonymous questionnaire. The questionnaire was completed in the examining room without the parents being present. These patients were being evaluated for illnesses as well as receiving routine health maintenance evaluations. They were not being evaluated for drug-related problems. The questionnaire asked if they had ever tried alcohol, marijuana, or other drugs, and if they used such drugs on a regular basis. The definition of "regular basis" in this study was defined as once a month or more. Tables 1 and 2 provide the statistics in regard to drug usage by age and sex.

Comment.—As expected, the older the adolescent, the more likely he or she used alcohol or other drugs, either on a trial or regular basis. Surprisingly, however, female adolescents began experimenting with alcohol and a variety of drugs at an earlier age than

Table 1.—Drug Usage 'Ever'

Sex/Age, y	No. of Patients	Drug, No. (%) of Subjects		
		Alcohol	Marijuana	Other*
M/12	2	2 (100)	0	0
F/12	1	0 (0)	0	0
M/13	15	6 (40)	0	0
F/13	8	5 (62)	2 (24)	C 1 (12)
M/14	19	11 (51)	4 (21)	C 13 (5) LSD 1 (5)
F/14	20	15 (75)	9 (45)	C 3 (15) LSD 2 (10) M 3 (15)
M/15	21	17 (80)	6 (28)	0
F/15	25	23 (92)	10 (40)	C 4 (17) LSD 3 (12) M 3 (12) P 2 (8)
M/16	17	17 (70)	12 (81)	C 4 (23) LSD 2 (10) M 5 (29) A 1 (6)
F/16	23	15 (65)	8 (34)	C 2 (9) LSD 1 (4) M 2 (9) PCP 1 (4)
M/17	18	17 (94)	12 (67)	C 4 (22) M 4 (22) AN 1 (6)
F/17	18	17 (94)	12 (67)	C 4 (22) LSD 3 (17) M 4 (22) Ph 1 (6)
M/18	11	10 (91)	8 (73)	C 4 (36) LSD 1 (9) M 2 (18) Ph 1 (9)
F/18	5	5 (100)	5 (100)	C 2 (40) 1 (20) 2 (20)

*C indicates cocaine; M, methamphetamine; P, pencyclidine; A, amphetamine; AN, amyl nitrate; and Ph, pheniclyclidine.

Table 2.—Regular Drug Usage

Sex/Age, y	No. of Patients	Drug, No. (%) of Subjects		
		Alcohol	Marijuana	Other*
M/12	2	0	0	0
F/12	1	0	0	0
M/13	15	0	0	0
F/13	8	1 (12)	0	0
M/14	19	1 (5)	1 (15)	0
F/14	20	3 (15)	2 (10)	C 1 (5) M 1 (5)
M/15	21	5 (23)	2 (10)	0
F/15	25	7 (24)	0	0
M/16	17	7 (41)	3 (18)	M 2 (12)
F/16	23	7 (30)	1 (4)	M 1 (4)
M/17	18	10 (56)	1 (6)	0
F/17	18	6 (33)	5 (28)	LSD 1 (6) M 1 (11)
M/18	11	8 (73)	1 (9)	0
F/18	5	3 (60)	0	0

*C indicates cocaine; M, methamphetamine.

did male adolescents and continued to do so up until 18 years of age. It is not known whether this trend continues beyond this age since we did not survey patients older than age 18 years.

Do female adolescents experiment with drugs at an earlier age because of their earlier age of onset of puberty with all of the physical and emotional turmoil that puberty entails? Are female adolescents being exposed to drugs at an earlier age because of our societal dating patterns (usually involving an older male adolescent rather than one of the same age as the female adolescent)? Does this now mean that female adolescents have a higher risk-taking potential for drug usage than male adolescents? Certainly, it has been traditionally taught that boys display more risk-taking behavior than girls, but does this occur at a later age? Is this now changing in our society at least as drug usage is involved? These questions cannot be answered by this small, limited study.

Another disturbing point of this study involves the resurgence of the use of LSD. This drug was popular in the early 1960s and seems to be again gaining popularity. Will we start seeing more problems related to intoxication with this substance? Perhaps by knowing what age group use drugs and what drugs are being used by the adolescent patients in our own practices, we can become more successful at intervention. However, it must be emphasized that the information obtained from this population of adolescents may not apply to other pediatric/adolescent practices. Since female adolescents (at least in my practice) are experimenting with drugs at an earlier age than male adolescents, it might be beneficial to target girls at a younger age for preventive drug programs. Unfortunately, statistics on nicotine use were not obtained, although this substance clearly belongs in the category of drug abuse.

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Reconsideration of IgM-Enriched Intravenous Immunoglobulin for Neonatal Sepsis

To the Editor.—In the article by Haque et al¹ in the December 1988 issue of *AJDC*, the authors concluded that mortality from neonatal sepsis (suspected or proved) was significantly reduced in a group of 30 infants treated in a prospective, randomized trial with IgM-enriched intravenous immunoglobulin (Pentaglobin, Biotest Pharma, Frankfurt, West Germany) in addition to antibiotics compared with a control group of 30 infants who were treated with antibiotics alone.

Their conclusion of a statistically significant ($P < .001$) reduction in mortality between the treated and control groups was based on the use of Student's *t* test for statistical analysis. Is there some rationale that makes use of the Student *t* test the appropriate test for analysis of these outcome data?

As outcome is a discrete and not a continuous or numerical parameter, a *t* test, which is a parametric test of the difference in means between two samples or two groups, is not the proper test to apply to this analysis. Rather, a nonparametric test is indicated, as outcome can be categorized as the proportion of infants in each group who lived vs those who died. Reorganization of their Table 2 into a 2×2 contingency table would appear as follows:

Group	Lived	Died
Control (n = 30)	24	6
Immunotherapy (n = 30)	29	1

Using Fisher's Exact Test, because the expected frequencies in some of the cells are less than 5,² and a two-sided test, because there is no strong basis for predicting which way the test should turn out, the level of significance is $P = .10$ (Statpak 4.1, Northwest Analytical Inc, Portland, Ore). The failure to reach statistical significance at $P < .05$ using Fisher's Exact Test in this case may be due to a β

error from too small a sample size; that is, the failure to find a significant difference in outcome among treated and control infants, if the treatment did in fact make a difference, could be overcome by studying a larger population of infants.

However, if the Fisher Exact Test is applied to evaluate differences in outcome among only infants with proved sepsis, then $P = .40$.

While the idea to use IgM-enriched intravenous immunoglobulin to treat neonatal sepsis is an interesting variant on the idea of using standard, commercially available intravenous immunoglobulin for the same purpose, Haque et al have not provided convincing data regarding the efficacy of the preparation studied. Further studies are warranted before adopting IgM-enriched intravenous immunoglobulin as part of a therapeutic armamentarium against neonatal sepsis.

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In Reply.—I am grateful for Dr Hall's interest in our work. Indeed, the reason for not using the Fisher Exact Test was that our sample size was too small for each cell.

We do not claim that we have proved the efficacy of IgM-enriched intravenous immunoglobulin in the treatment of neonatal sepsis. What we have tried to show is that this modality helps in improving the outcome but needs to be confirmed by larger studies. We are now comparing intravenous immunoglobulin with IgM-enriched intravenous immunoglobulin in the treatment of neonatal sepsis.

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Leads From the MMWR

Morbidity and Mortality Report
Centers for Disease Control, Atlanta

Firearm-Associated Homicides Among Family Members, Relatives, or Friends—Ohio

IN 1985, 311 (56%) of 553 homicides in Ohio occurred among relatives or acquaintances; 191 (61%) of these 311 homicides involved the use of firearms (Federal Bureau of Investigation (FBI), unpublished data, 1985). To learn more about firearm homicide among persons who are closely acquainted, the Ohio Department of Health (ODH), Division of Epidemiology interviewed offenders involved in homicides occurring between 1982 and 1985 that met the following six criteria: the homicide 1) occurred in Cleveland, Cincinnati, Columbus, Toledo, Dayton, or Akron; 2) occurred between family members, relatives, or friends; 3) was committed with a firearm kept in the household; 4) victim and offender were greater than or equal to 18 years of age; 5) occurred in or within the immediate vicinity of a residence; and 6) was not secondary to another crime. The primary purposes of the investigation were to describe demographic characteristics of the offenders and to identify situational or environmental factors related to the homicide.

Using records from the Ohio State Department of Corrections and Rehabilitation and police records from Cleveland, Cincinnati, and Columbus, investigators identified 105 homicides that met the above criteria. Of these, interviews were completed with 50 (48%) offenders. Of the 55 offenders who were not interviewed, 37 (67%) could not be located, 12 (22%) refused to participate, and three (5%) had died. Three (5%) interviews were not completed for other reasons.

Since the Ohio Homicide study included only a subset of firearm-associated homicides that occurred among family members, relatives, or friends, selected offender characteristics were compared with Ohio data from the FBI. The distribution from the Ohio homicide study approximates Ohio estimates from the FBI for median age

of the offender and type of firearm used in the homicide (FBI, unpublished data, 1985). However, in the Ohio homicide study, offenders were less likely to be male and less likely to be white.

Offenders' responses varied widely as to their perception of the single immediate cause of the homicide. Forty percent responded that some type of threatened (30%) or actual (10%) physical abuse was occurring just before the incident, regardless of whether the victim or the offender initiated the abuse. Ten percent suggested that alcohol and/or drugs was the immediate reason for the incident. Other reasons for the incident included "jealousy," "money," or "the general stresses of living together" (10%), "accidental" (12%), "other" (10%), or "unknown" (18%).

Handguns were the type of firearm used in 76% of the homicides. Less than half the offenders reported owning the firearm; only 26% reported that the weapon was purchased from a licensed dealer. Fifty-six percent of firearms were kept in the bedroom; 96% were always kept in the household in which the homicide occurred, and the remaining 4% were usually kept in the household. Self-protection was the most commonly reported (56%) purpose for obtaining the firearm.

Sixty-four percent of the firearms were always kept loaded, and at least 64% were always kept in an unlocked location. Forty-four percent were always kept loaded and in an unlocked location. Thirty-eight percent of the firearms had been owned less than 1 year; 66% had been owned ≤ 6 years.

Alcohol was reported to have been consumed before the incident by 62% of the offenders, and alcohol and/or drugs, by 88% of the offenders and/or victims. Thirty percent of the offenders had the firearm in their immediate physical possession just before the

incident; 54% reported drawing a firearm or some other weapon first, and 22% reported the victim drew a firearm or some other weapon first. Thirty-eight percent believed they could not have resolved the situation without the firearm, and 22% responded that the victims "dared" them. Forty-eight percent reported they did not intend to shoot the victim when they drew the weapon. Forty percent indicated that the victim was approaching them when the gun was fired, and 48% fired the weapon within 15 seconds of brandishing it. Seventy percent of the offenders reported never practicing shooting firearms; 50% recalled that their parents had owned a firearm during their childhood. Seventy-four percent indicated that just before or during the incident they did not consider that they could go to prison for using a gun.

CDC Editorial Note: This investigation by the ODH helps describe the problem of firearm-associated homicide in Ohio. Homicide is the fourth leading cause of years of potential life lost before age 65 in the United States and fifth in Ohio¹ (ODH, unpublished data, 1987). In 1985, 59% of all U.S. homicides involved relatives and acquaintances.² In Ohio, between 1979 and 1986, 63% of all homicides were committed with a firearm (ODH, unpublished data, 1988).

The findings in this investigation should be interpreted with caution because the sample size was limited and restricted to homicides in six urban areas and because the sample size was further reduced as a function of the number of offenders who could be included in the study. In addition, this study investigated homicides between family members, relatives, or friends, and the results may not be generalizable to other types of homicide.

However, the results from this investigation are useful in planning future investigations of possible risk

factors for firearm-associated homicide among family members, relatives, or friends. If confirmed by future research, these findings may represent possible avenues for intervention to prevent firearm-associated injuries.

Four areas of study have been identified for further efforts in developing effective strategies to prevent firearm-associated injuries: 1) collection of information on the magnitude, characteristics, and costs of the morbidity and disability caused by firearms and

on the types of firearms that inflict these injuries; 2) determination of the number, type, and distribution of firearms in the United States; 3) conduct of epidemiologic studies that quantify the individual risks of injury associated with the possession of firearms; and 4) evaluation of interventions related to firearms. Pursuit of such research strategies should improve the scientific base of information needed for further research and prevention efforts.

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Influenza Vaccine Composition Recommendation for the 1989-90 Season

During the 1988-89 influenza season, influenza type B has predominated in the United States but has cocirculated with type A(H1N1) and A(H3N2). Elsewhere in the Northern Hemisphere, type A influenza has generally predominated, with both influenza A(H1N1) and A(H3N2) cocirculating.

Antigenic analysis of type A(H1N1) viruses from outbreaks indicates that most strains are closely related to the U.S. vaccine strain, A/Taiwan/1/86. The antibody induced by this vaccine component reacts well with the recently circulating type A(H1N1) viruses.

As in last season, type A(H3N2) viruses continue to be heterogeneous. Some isolates resemble the current vaccine strain A/Sichuan/2/87, but most are better inhibited by antiserum to the A/Shanghai/11/87 reference virus. In addition, patients vaccinated with A/Sichuan/2/87 vaccine consistently had lower antibody responses to the A/Shanghai/11/87 strain than to the vaccine strain.

Most influenza B strains isolated this season, particularly in the United States, are similar to the current vaccine component, B/Victoria/2/87. However, a new variant was identified in Asia; B/Yamagata/16/88 is an example of the variant. This strain was first seen in the People's Republic of China in August 1987 and circulated in Japan, Hong Kong, Singapore, Taiwan, and

Thailand from February 1988 to January 1989. The antibody induced by the current B/Victoria/2/87 vaccine component is poorly reactive with the B/Yamagata/16/88 strain.

Based on these and other data, the World Health Organization (WHO) has recommended that the trivalent influenza vaccine for use in the 1989-90 season contain the following components: type A(H3N2), A/Shanghai/11/87-like antigen, and type B/Yamagata/16/88-like antigen and retain the type A(H1N1) component of the current vaccine. This decision has been ratified by the Food and Drug Administration's Vaccine Advisory Panel.

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CDC Editorial Note: Influenza type A viruses are classified into subtype on the basis of two antigens: hemagglutinin (E) and neuraminidase (N).

Three subtypes of hemagglutinin (H1, H2, H3) and two subtypes of neuraminidase (N1, N2) are recognized among influenza A viruses that have caused widespread human disease. Immunity to these antigens, especially the hemagglutinin, reduces the likelihood of infection and the severity of disease if infection occurs. However, over time there may be enough antigenic variation (antigenic drift) within the same subtype that infection or vaccination with one strain may not induce immunity to distantly related strains of the same subtype. Antigenic variation occurs with influenza B viruses, although no subtypes are known to exist. For these reasons, major epidemics of respiratory disease caused by new variants of influenza continue to occur. The antigenic characteristics of current strains provide the basis for selecting virus strains included in each year's vaccine.

The manufacturing, quality control, and distribution process involved in producing about 30 million doses of influenza vaccine in the United States require many months to complete. Therefore, the decisions on which strains to include in the vaccine formulation for the 1989-90 influenza season were to be completed by late March to early April of 1989. Specific recommendations by the Immunization Practices Advisory Committee will be available later this spring.

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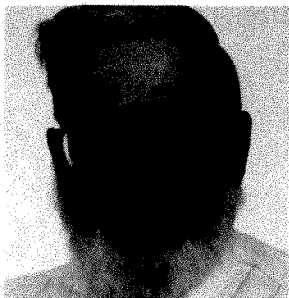
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The Editorial Board Speaks . . .

George W. Brown, MD



George has been a most valuable member of our board. He often characterizes himself as a "drudge," "maven," or "curmudgeon," but he is anything but these descriptors to the Editor. George has the facility of making statistics understandable to the rest of the world, a tremendous asset to the Editorial Board and Editor. In addition, he has the uncanny knack of delving into a report and identifying and analyzing not only the statistical treatment, but the entire methodologic approach that the author(s) used. His comments are trenchant, utilitarian, and tinged with enough humor for authors and editors to enjoy, but not so much that the main message is diluted. In short, he is that rare person, a useful referee to authors of both accepted and rejected manuscripts from whom we constantly receive laudatory remarks concerning his commentaries.

PRAISE FOR USEFUL WORDS

A clerk brags to the boss, "I am *precise* in parking my car; it is always in the exact center of the space." The boss responds, "Yes, but you are not *accurate*; you often park in my space."

Some familiar and useful words may lead to discussion such as this when the words have a variety of meanings. *Precise* ordinarily means meticulous or fastidious; to a machinist it implies a closely fitted machine part. In a laboratory, *precision* may denote the exactness of a measurement (eg, glucose within 0.1 mmol/L), or it may relate to the number of significant digits used (eg, 5.1 mmol/L or 5.12 mmol/L). In some contexts *precision* implies the closeness (consistency) of repeated measurements of the same substance or object. If systematic error (bias) is present, repeated measurements may be closely clustered, but displaced from the truth, ie, they are *precise* but *inaccurate*. This was the problem with the clerk and parking.

Statisticians use *precision* to describe the dispersion or variability of a set of measurements, often expressed as the SD. Repeated measurements of the same thing should be distinguished from measurements of several things or of the same thing at different times.

Because of these vagaries of meaning, Feinstein¹ suggests that *precision* may be too ambiguous for scientific communication; he recommends *consistency*, especially in clinical situations. Others use *dependable*, which also has several meanings: durable, steadfast, predictable, credible, and so on. *Dependable* is probably not precise enough for scientific usage.

A word often seen alongside *precision* is *accuracy*. It usually means nearness to the truth, that is, to the correct value. Statisticians use *accuracy* to describe an estimate (from observations) of some parameter in relation to its true value. They also describe values that are free from systematic error (bias) as being *accurate*. There are fewer ambiguities associated with *accuracy* than with *precision*. Even if we are careful with these words, we still confront two others with varying meanings: *reliability* and *validity*.

In technical writing, *reliability* is used in three different ways. Among scholastic test-makers and psychologists,² *reliability* implies the internal consistency, the connectedness of the items in a multi-item test or psychologic instrument. It is a measure of how well the separate elements relate to the trait or factor being evaluated.

Feinstein¹ discusses the theory, development, and use of clinical rating scales, a field he has named "Clinimetrics." In pediatrics, a familiar example is the Apgar score. In psychiatry,³ there is also much concern with the inconsistencies in diagnosis and classification. In these contexts *reliability* is used in two ways: (1) Does the same observer get the same results on repeated observations of the same thing (test-retest or within-rater reliability)? (2) Do different observers see the same thing when they examine the same object or event (interrater reliability)? For example, reliability checks can be done on Apgar scoring (of the same infant) among several raters: nurse, obstetrician, anesthetist, and pediatrician. Test-retest reliability might be evaluated by comparing Apgar scores by the same observer shown the same videotape of a distressed infant on different occasions. Psychiatry has struggled with charges that diagnoses of mental illness lack both test-retest and interrater reliability.

Reliability is similar in meaning to *precision* (or *consistency*).

Validity is a kind of well-established *accuracy*; it concerns the truthfulness of the outcomes of the endeavor. *Validity* is frequently accompanied by an adjective. *Internal* validity touches on the methods, controls, randomization, and so on within an experiment used to assure that the results are credible and persuasive. But the results may not apply to subjects outside the experiment. *External* validity implies that results can be generalized from the sample studied to the population from which the sample came.

Face validity refers to the immediate "common sense" evaluation applied to a research effort. Is there surface credibility? Are the things measured sensibly related to the goals of the effort? For some of us, astrology lacks face validity. *Content* validity relates to the elements included or not included in a project. Should a test of reading skills be included in assessment of musical talent? *Construct* validity addresses the fit of the observations to already formed ideas (constructs) about the matters under study. Does the construct "intelligence" include manual dexterity? Reaction time?

In biomedical contexts, validity is often *criterion-related*; that is, do observations correspond to an established criterion or "gold standard." An academic achievement test has criterion validity if it matches actual performance, say grade point average. Physical diagnosis of a fracture has criterion validity if the roentgenogram confirms the fracture.

Criterion validity comes in two versions. *Predictive* validity concerns the accuracy with which measurement of some current element or property predicts a future characteristic. Does the Denver Developmental Screening Test⁴ at age 4 years predict neurodevelopmental integrity at age 8 years? The other version of *criterion* validity is *concurrent* validity, the extent to which a measurement of a trait or element is related to some other measurement done at the same time. Does a new quick test for streptococci agree with throat culture results?

Apgar scores have good *concurrent* validity regarding the need for resuscitation, but *predictive* validity for later impairment is poor. The validity of diagnostic tests may be described in terms of test sensitivity, specificity, and predictive accuracy, topics too complex to discuss here.

This is a sketchy look at some familiar but capricious words. They occur often in our professional literature, and their usefulness is unquestioned. For me, when professional reading begins to get tiresome, a pleasant change of pace can be achieved by poking around in the language to see how these praiseworthy words are being used—or misused.

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Elevated Serum Levels of Tumor Necrosis Factor Are Associated With Progressive Encephalopathy in Children With Acquired Immunodeficiency Syndrome

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• The cytokine tumor necrosis factor (TNF) was assayed in the sera ($n=31$) and cerebrospinal fluid ($n=26$) of children with acquired immunodeficiency syndrome, using a competitive radioimmunoassay. Elevated serum levels of TNF were found in 15 (79%) of 19 patients with progressive encephalopathy (PE), compared with 1 (8%) of 12 patients without neurologic involvement. There was a significant association of PE with elevated serum TNF levels. Conversely, of 16 patients with elevated serum TNF levels, 15 (94%) were found to have PE, and of 8 patients with serum TNF levels greater than 100 pg/mL, all 8 (100%) had PE. No association was found between cerebrospinal fluid levels of TNF and PE. Neither serum nor cerebrospinal fluid TNF levels correlated with the degree of cachexia. These data suggest that circulating TNF may be responsible for the myelin damage that occurs in human immunodeficiency virus type 1-associated PE.

(AJDC. 1989;143:771-774)

Tumor necrosis factor (TNF), a macrophage/monocyte-derived immunomediator¹ (also known as cachectin) is a cytokine that mediates both beneficial and cytotoxic events.^{2,3} It has been implicated as a mediator of septic shock,^{4,5} cachexia,^{6,7} graft-vs-host disease,⁸ and death in animals with cerebral malaria.⁹

It is also associated with a poor outcome in meningococcemia¹⁰ and pediatric purpura fulminans.¹¹ Elevated levels have been observed in human parasitic infection,¹² neoplastic disease,¹³ and adult patients with acquired immunodeficiency syndrome (AIDS) with secondary infection.¹⁴

The human immunodeficiency virus type 1 (HIV-1) has been identified as the cause of AIDS in adults and children.¹⁵ In vitro, it has been shown that HIV-1-infected mononuclear cells produce a factor cytotoxic to L929 cells, a fibroblast cell line sensitive to the lethal effects of macrophage-derived TNF.¹⁶ Supernatants from monocyte cultures of symptomatic HIV-1-infected patients produce sevenfold greater levels of TNF compared with control subjects and much higher levels than asymptomatic HIV-1-infected patients.^{17,18}

Children with AIDS often develop a progressive, debilitating encephalopathy.¹⁹ The clinical hallmarks include loss of developmental milestones or dementia and pyramidal tract signs, with the pathologic features of severe white matter degeneration, inflammatory cell infiltrates with macrophages and multinucleated giant cells,²⁰ and radiologic and pathologic features of cerebral atrophy.¹⁹ The pathogenesis of this condition has remained elusive and speculative.

Recently, Selmaj and Raine²¹ demonstrated that TNF, in vitro, led to the destruction of oligodendrocytes, which led to speculation that TNF may be involved in processes of white matter destruction. In vitro experiments have demonstrated that stimulated rat astrocytes release a cytotoxic factor that kills L929 cell targets and rat oligodendrocytes, as does recombinant human TNF

(r-Hu-TNF). Taken together, these observations suggest that stimulated astrocytes may produce TNF.²² Therefore, cytotoxic factors, such as TNF, released by HIV-1-infected invading inflammatory cells of monocyte/macrophage lineage or resident microglia, may be involved in the white matter damage associated with HIV-1 infection.^{23,26}

Many children with pediatric AIDS exhibit failure to thrive and a progressive cachexia.²⁶ It has been proposed that wasting or cachexia may also be a TNF-mediated event.⁶ Therefore, we have investigated levels of TNF in the serum and cerebrospinal fluid (CSF) of HIV-1-infected children with or without progressive encephalopathy (PE) or wasting.

METHODS

Specimens of sera ($n=31$) and CSF ($n=26$) from children with AIDS, aged 6 months to 17 years (mean, 4.1 years), stored at -70°C , were assayed for TNF; 25 specimens were matched. Specimens were collected as part of ongoing studies of HIV-1 infections in children. All of the patients fulfilled the Centers for Disease Control, Atlanta, Ga, criteria²⁷ for pediatric AIDS. Using previously described clinical criteria,^{19,20} each child was diagnosed as having either PE (22 patients provided 19 sera and 18 CSF samples), or no PE (NPE) (14 patients provided 12 sera and 8 CSF samples). Briefly, all children with HIV-1 infection at our institution were classified into one of the following three categories:

1. *Normal neurologic findings.*

2. *Static encephalopathy.*—These children had developmental delay or motor deficit that was nonprogressive and had normal brain growth. Static encephalopathies occurred frequently in our patient population prior to the appearance of HIV-1 infection and were most often due to premature birth, intrauterine exposure to drugs or other in-

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fectious agents, or genetic factors.

3. *Progressive encephalopathy.*—These children had a loss of developmental milestones or intellectual abilities (19 of 22 patients with PE), progressive deterioration of motor function (21 of 22 patients), and/or impaired brain growth (20 of 22 patients). Impaired brain growth was documented by serial head circumference measurements or by serial computed tomographic scans.

Progressive encephalopathy was considered to be associated with HIV-1 brain infection. Children with static encephalopathy, and those with normal neurologic examination findings, were combined to form the NPE group.

These patients were further classified as being cachectic or noncachectic. Cachexia was defined as a weight quotient (weight age [age for which patient's weight is in the 50th percentile]/chronologic age of the patient) of less than 0.6. Patients were further subgrouped according to the presence or absence of secondary infections, defined as *Pneumocystis carinii* pneumonia, disseminated *Mycobacterium avium-intracellulare* or cytomegalovirus, *Candida albicans* esophagitis, chronic salmonellosis, pyogenic bacterial infections, cryptococcosis, or toxoplasmosis.²⁸ For comparison, controls were provided from sera and CSF from three children with inflammatory/infectious-associated neurologic illness (one patient with encephalitis and two patients with myelitis), providing four sera and five CSF samples; four children with noninflammatory neurologic disorders (acute infantile hemiplegia, functional disorder, central nervous system leukemia, and simple febrile seizure), providing three sera and four CSF samples.

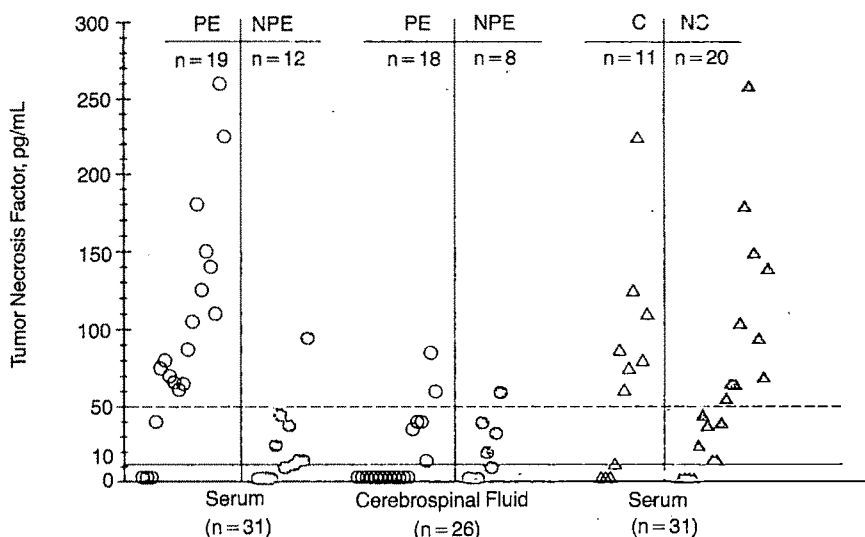
A competitive radioimmunoassay (Medgenix, Brussels, Belgium; distributed by Cambridge Medical Technology, Billerica, Mass) was used for the TNF assay. One hundred microliters of rabbit antiserum, raised against r-Hu-TNF, was incubated for 18 hours at room temperature with either 100 μ L of patient serum or CSF, standard (known concentrations of r-Hu-TNF), or control. Subsequently, 100 μ L of r-Hu-TNF labeled with iodine 125 was added and incubated for 4 hours at room temperature. Antirabbit gammaglobulin, raised in goats, mixed with polyethyleneglycol, was then added (1 mL of solution), and, after a 20-minute incubation at room temperature, all the ¹²⁵I-r-Hu-TNF-antibody complex was precipitated.

After centrifugation, the polyethylene glycol-bound radioactivity was determined. A standard curve was constructed, and the TNF concentrations of the samples were determined by interpolation from this curve. Samples were run in duplicate determinations, with obvious outliers (2 of 174 determi-

Serum Tumor Necrosis Factor (TNF) Levels and Neurologic Status in Pediatric Patients With Acquired Immunodeficiency Syndrome*

Serum TNF Level	No. of Patients	
	Progressive Encephalopathy	No Progressive Encephalopathy
>50 pg/mL (elevated)	15	1
<50 pg/mL (not elevated)	4	11
Total	19	12

*Using Fisher's Exact Test, comparing the number of patients with progressive encephalopathy with patients without progressive encephalopathy with elevated TNF levels, a significant association was found for progressive encephalopathy and elevated TNF levels ($P<.001$).



Tumor necrosis factor levels in the serum and cerebrospinal fluid of children with acquired immunodeficiency syndrome. Elevated tumor necrosis factor levels are greater than 50 pg/mL; the limits of detectability are 10 pg/mL. PE indicates progressive encephalopathy; NPE, no progressive encephalopathy; C, cachexia; and NC, no cachexia.

nations) eliminated. Sample concentration determinations were obtained using a log representation of $B/B_0 \times 100$ as a function of the TNF concentration $\{B/B_0[(\text{counts of standard or sample}) - (\text{counts nonspecific})]/[(\text{counts of the zero standard}) - (\text{counts nonspecific})]\}$, and double-checked with an arithmetic representation of counts vs TNF concentrations of standards. The assay employed was standardized against known concentrations of r-Hu-TNF. The interassay and intra-assay coefficients of variation were less than 10%.

Results were expressed as picograms per milliliter. The limit of detection was 10 pg/mL, and greater than 50 pg/mL was considered elevated. Statistical analysis consisted of Fisher's Exact Test, two-tailed.

RESULTS

Among children with AIDS, elevated serum TNF levels (>50 pg/mL) were

found in 15 (79%) of 19 patients with PE, and only 1 (8%) of 12 patients with NPE. Overall, there were 16 patients with elevated serum TNF levels and 15 (94%) of 16 had PE. Of 8 patients with serum TNF levels greater than 100 pg/mL, all 8 (100%) had PE. Of the patients with PE and elevated TNF levels, 5 (33%) of 15 had a concomitant secondary infection. Using Fisher's Exact Test, PE was significantly associated with an elevated serum TNF level ($P<.001$), and, alternatively, an elevated serum TNF level was significantly associated with PE ($P<.001$) (Table).

Of 26 CSF samples, TNF was detected in 6 (33%) of 18 patients with PE and 5 (63%) of 8 with NPE (Figure). Of patients with PE, 2 (11%) of 18 had CSF TNF levels greater than 50 pg/mL, compared with 1 (13%) of 8 with NPE.

There was no significant association between CSF TNF levels and the presence of PE.

The only child in the NPE group with elevated TNF levels in serum and CSF died 5 months after the sample was obtained of a rare manifestation of HIV-1 infection, namely, leiomyosarcoma of the intestine. The brain at postmortem examination showed metastatic tumor but no inflammatory or white matter changes routinely found in children with HIV-1-associated PE.

Among patients with noninflammatory neurologic disorders, neither sera ($n=3$) nor CSF ($n=4$) exhibited elevated TNF levels (two samples of sera with undetectable levels and one sample with 45 pg/mL; two samples of CSF with undetectable levels and two samples with 30 pg/mL).

For patients with inflammatory neurologic disorders, there were four sera specimens from two patients and five CSF specimens from three patients. One patient with a diagnosis of encephalitis had no TNF elevation in the CSF. The two patients with myelitis had elevations in both the serum and CSF TNF levels. One of these patients had a varicella-associated myelitis, demonstrating a greater than twofold rise in serum and CSF TNF levels during an acute exacerbation—from 50 to 125 pg/mL in the sera, and 60 to 140 pg/mL in the CSF—and a return to undetectable levels during convalescence.

Of the 31 pediatric patients with AIDS, 11 were defined as cachectic and 20 as noncachectic. Of the cachectic patients, 7 (64%) of 11 had elevated serum TNF levels, and of the noncachectic patients, 10 (50%) of 20 had elevated levels. There were three CSF specimens greater than 50 pg/mL: two subjects were classified as cachectic, and one as noncachectic. There was no significant association between serum or CSF TNF levels and the presence of cachexia (Table).

COMMENT

The levels of TNF obtained in the HIV-1-infected children's sera are of a magnitude observed in other pathologic conditions. Scuderi et al¹² found patients with malaria and kala-azar with a mean of 119 pg/mL; Waage et al¹⁰ found that a level greater than 100 pg/mL of TNF in

patients with meningococemia indicated a poor outcome; Teppo and Maury,¹³ using a radioimmunoassay similar to the assay used in this study, demonstrated mean levels of 45 pg/mL in parasitic disease, 84 pg/mL in neoplasms, 20 pg/mL in rheumatoid arthritis, and 305 pg/mL in acute bacterial infections. Normal individuals have consistently undetectable or exceedingly low serum TNF levels.^{14,28} Likewise, we have found no elevated levels in control subjects with noninflammatory neurologic disorders.

In our present study, PE seen in pediatric HIV-1 infection was strongly associated with elevated serum levels of TNF compared with the group of patients without neurologic disease. Despite this strong association, it is noteworthy that CSF TNF levels were not consistently found to be elevated in children with PE. Likewise, for patients with other neurologic diseases, CSF TNF levels were elevated only in acute inflammatory disorders, including a dramatic increase of TNF in a patient with myelitis who experienced an acute exacerbation. This further implicates a role for TNF in demyelinating processes *in vivo*, as suggested by *in vitro* experiments.²¹

"Normal" or "elevated" levels of TNF in the CSF are not known. One might expect that normal levels would approach zero, since, in the nonpathologic state, invading macrophages are not present in the nervous system and resident immunologic cells are not activated. Thus, it is not surprising that the highest CSF levels were obtained during an acute, inflammatory myelitis, and in a more chronic, degenerative process, such as the slow PE of AIDS, elevations of CSF TNF were infrequently observed.

The collection technique (ie, the inability to immediately freeze the specimen or the age of the specimen [some specimens were 2 to 3 years old]) may have also contributed to a loss of measurable TNF activity. Thus, "elevated" levels of TNF in the CSF may be lower in magnitude compared with levels in serum and may have been found under conditions that maximize preservation of TNF activity. There may also be a dilution effect in the CSF, partially masking a locally acting effect of cyto-

kines. Evidence for the presence of TNF in the white matter could be provided by immunohistologic staining of the brain for TNF, as Breder et al²⁹ have demonstrated for interleukin 1 in the hypothalamus. Resident brain microglia, reported to be infected by HIV-1,²⁸ may be an additional source of TNF.

Tumor necrosis factor in the serum may cross the blood-brain barrier and cause myelin damage, even if only low levels are detected in the CSF. This would be consistent with the observed association of high serum TNF levels with PE. Alternatively, elevated serum levels of TNF may only reflect an advanced state of disease or result from concomitant infection.¹⁴ In this study, among patients with elevated serum TNF levels and PE, the finding of a concurrent secondary infection was not sufficient to account for the elevated levels.

Hesse et al⁶ have shown that humans can withstand a transient, marked elevation of TNF, but persistently elevated TNF levels may precipitate pathologic and adverse events.⁷ A sustained toxic effect of TNF on myelin²¹ could result in cumulative white matter damage as identified in neuropathologic studies of PE.²⁰ The toxic effects of TNF may represent excessive expression of a normally beneficial immune response due to the deregulation, by antigenic stimulation or proviral induction, of a normally tightly regulated gene.³⁰

Our present study reveals a significant association between elevated serum TNF levels and the PE seen in children with AIDS. Hence, TNF may provide the link between HIV-1 infection, inflammation, and white matter damage underlying PE. Secondary infections alone could not account for these elevations. The TNF found in the CSF bore no relationship to the presence of PE. No significant association was found between serum or CSF TNF levels and the cachexia associated with pediatric AIDS.

Further studies are needed to establish CSF norms for TNF; to prospectively measure TNF levels over time in an individual patient¹⁴ and its relationship to the course of neurologic illness in pediatric AIDS; to elucidate interactions between TNF and other cytokines, such as interleukin 1, interferon-

gamma, and lymphotoxin, in pediatric AIDS; and to assess local effects of TNF in tissues, such as the brain, which may be sites of cytokine-mediated pathology.

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In Other AMA Journals

ARCHIVES OF GENERAL PSYCHIATRY

Cerebral Glucose Metabolism in Childhood-Onset Obsessive-Compulsive Disorder

Susan E. Swedo, MD; Marc B. Schapiro, MD; Cheryl L. Grady, PhD; Deborah L. Cheslow; Henrietta L. Leonard, MD; Anand Kumar, MD; Robert Friedland, MD; Stanley I. Rapoport, MD; Judith L. Rapoport, MD (*Arch Gen Psychiatry*. 1989;146:518-526)

Prognostic Factors and Life Expectancy in Children With Acquired Immunodeficiency Syndrome and *Pneumocystis carinii* Pneumonia

P 24, 242

Larry J. Bernstein, MD; Michael R. Bye, MD; Arye Rubinstein, MD

• Eighteen children with the acquired immunodeficiency syndrome (AIDS) were diagnosed as having *Pneumocystis carinii* pneumonia (PCP) by either open lung biopsy or bronchoalveolar lavage. Seven patients (39%) died during the acute illness. Alveolar-arterial oxygen gradients at the time of presentation and lactate dehydrogenase levels did not distinguish survivors from nonsurvivors. Total lymphocyte and T4 cell counts were low in children who died during the initial PCP infection but had considerable overlap with survivors. Response to phytohemagglutinin was measured in 5 of the 7 patients who died initially. In these patients, the mean phytohemagglutinin response was 1977 cpm. Of the 11 early survivors, 10 died within 27 months after PCP. Mean phytohemagglutinin response was 46 079 cpm in patients who died within 1 year, and 44 768 cpm in those who died later. Only 1 child is still alive 5 years after PCP illness. Children with AIDS and PCP infection have high initial mortality and poor long-term prognosis. Response to phytohemagglutinin is helpful in predicting who will survive initial PCP infection.

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Pneumocystis carinii pneumonia (PCP) is the most common opportunistic infection in adults with acquired immunodeficiency syndrome (AIDS), occurring in over half the patients with the syndrome.¹ In addition, it is found in over 80% of individuals with AIDS who present with pulmonary infection.² *Pneumocystis* has previously been described in children with AIDS as well,³ presenting as an acute or subacute illness with fever, cough, and gradually

increasing respiratory distress. Clinical findings include wheezing, rhonchi, increasing hypoxemia, and isomorphic elevation of the serum lactate dehydrogenase level. Radiological findings may vary from hyperaeration with clear lung fields to complete "white out" with a picture consistent with adult respiratory distress syndrome.

From 1983 to 1986, 18 children presented with documented cases of PCP. We describe the short- and long-term course for this group of children, as well as laboratory variables that may play a role in predicting prognosis.

PATIENTS AND METHODS

All patients were followed up by the Division of Clinical Allergy and Immunology of the Albert Einstein College of Medicine, Bronx, NY. Serologic tests for human immunodeficiency virus type 1 (HIV-1) were performed on all patients, and included both enzyme-linked immunosorbent assay and Western blot assay. The diagnosis of PCP was pathologically confirmed in all cases. Prior to 1985, the diagnosis of PCP was made by the demonstration of *P carinii* organisms in specimens obtained by open lung biopsy. In subsequent years, the diagnosis was usually made by the identification of *P carinii* in bronchoalveolar lavage fluid. Bronchoscopy and lavage were performed by one of us (M.R.B.). Lactate dehydrogenase determinations were obtained on a standard 12-channel serial analyzer with an upper limit of 225 U. The T-cell enumeration was performed by monoclonal staining with OKT4 and OKT8 antibodies, and analysis on a fluorescent-activated cell sorter.⁴ Mitogenic responses to phytohemagglutinin (PHA), concanavalin A (ConA), pokeweed (PWM), and staphylococcal Cowan A, were measured by the incorporation of radioactive thymidine.⁴

RESULTS

Clinical Course

Eighteen patients were diagnosed as having PCP. The diagnosis of *Pneumo-*

cystis was made in eight patients by bronchoalveolar lavage, in eight patients by open lung biopsy, and in two patients at postmortem examination. Seven patients presented before 6 months of age, and in these children, PCP was their first clinical opportunistic infection. Six other children presented by 2 years of age. Only one child presented at older than 4 years of age. All patients were failing to thrive at presentation.

Seven patients died during the acute initial hospitalization for PCP (Fig 1). Six of the 7 were intubated for respiratory distress and died of progressive cardiopulmonary failure. Of the 11 remaining children who survived the initial PCP infection, 5 were intubated but were able to be weaned off a respirator. Follow-up of these 11 children revealed that 5 died within 12 months of PCP diagnosis, 1 died within 18 months, 3 died within 24 months, and 1 died at 27 months after PCP infection. Only 1 patient is still alive 5 years after PCP infection.

Six of the initial survivors developed histologically confirmed recurrence of PCP, all within 15 months of the initial illness. None received PCP prophylaxis at the time of recurrence. Four children died during the second illness. There were two cases of histologically proved disseminated cytomegalovirus in our initial total cohort and one of these died at the time of development of PCP.

Nine children developed *Mycobacterium avium-intracellulare* (MAI) infection. The diagnosis of MAI was made preceding PCP diagnosis in two patients, at the time of PCP diagnosis in two patients, and in the months after PCP infection in five patients. *Candida* sepsis was noted in two patients. Invasive *Candida* preceded PCP by several months in one child and had responded

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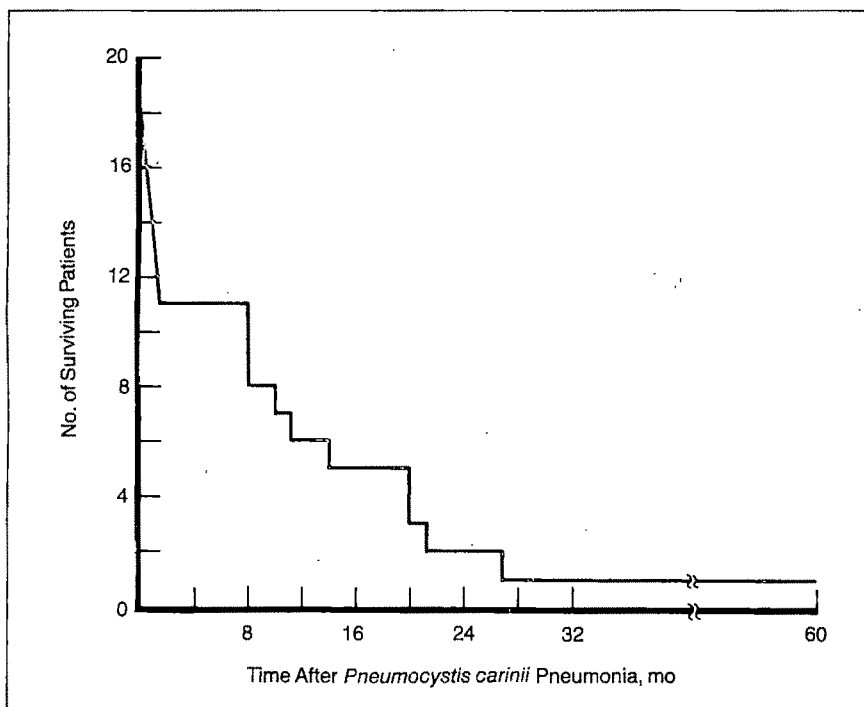


Fig 1.—Survival curve for 18 children with human immunodeficiency virus infection after onset of *Pneumocystis carinii* pneumonia.

to antifungal therapy long before PCP occurred. This child survived his initial PCP episode. A blood culture obtained shortly before death from a second child who died during the initial PCP episode yielded *Candida albicans*. This child was hospitalized for several weeks with multiple central lines, and his blood also yielded MAI.

In addition to recurrent PCP, factors contributing to poor outcome in the 10 early survivors included progressive MAI, progressive neuropathy, wasting syndrome, and, in 1 child, pulmonary hemorrhage secondary to idiopathic thrombocytopenia purpura. Two children died of acute pneumonitis without the identification of a pathogen.

Laboratory Findings

All patients had alveolar-arterial oxygen gradient of greater than 30 mm Hg at presentation. The range in room air PO_2 at presentation in survivors ranged from 45 mm Hg to 73 mm Hg. One additional child had an initial PO_2 value of 92 mm Hg on 35% inspired oxygen. The range of PO_2 in nonsurvivors was 34 mm Hg to 71 mm Hg at presentation. One child had a PO_2 of 87 mm Hg on 35%

inspired oxygen. Lactate dehydrogenase levels ranged from 320 to 2000 U/L with a mean of 922 U/L. There was no difference between survivors and nonsurvivors.

The mean total lymphocyte count was $1.4 \times 10^9/L$ (range, 0.4 to $2.6 \times 10^9/L$) in patients who died during the initial PCP episode. Values were $3.0 \times 10^9/L$ (range, 0.6 to $6.3 \times 10^9/L$) in patients who died within 1 year, and $3.3 \times 10^9/L$ (range, 1.0 to $6.9 \times 10^9/L$) in those surviving more than 1 year. Mean T4 cell count was $0.5 \times 10^9/L$ (range, 0.1 to $1.4 \times 10^9/L$) in nonsurvivors, $0.6 \times 10^9/L$ (range, 0.01 to $2.5 \times 10^9/L$) in patients who died within 1 year of PCP, and $1.0 \times 10^9/L$ (range, 0.2 to $1.7 \times 10^9/L$) in longer-term survivors. The PHA responses were markedly diminished in the children who died from the initial recurrence of PCP. The mean response was 1977 cpm with a range of 249 to 7006 cpm in the patients who died initially. The mean PHA response was 46 079 cpm (range, 11 687 to 103 701 cpm) in those who died within 1 year of PCP, and 44 768 cpm (range, 22 483 to 76 650 cpm) in those surviving longer than 1 year (Fig 2). While ConA, PWM, and

staphylococcal Cowan A responses were diminished in all children who died of the initial PCP infection, ConA response was decreased in 2 of 11 survivors, PWM in 6 of 11, and staphylococcal Cowan A in 6 of 9 measured.

COMMENT

Pneumocystis carinii pneumonia is associated with an acute mortality rate of 12% to 43% in adults with AIDS.^{2,5-7} Long-term survival (>3 years after PCP diagnosis) is unusual,⁸ although this may be modified with the advent of zidovudine therapy.⁹ There have been several studies in adults to determine prognostic factors for acute survival rates and ultimate life expectancy. Brenner et al¹⁰ reviewed 43 patients; an alveolar-arterial oxygen gradient of less than 30 mm Hg on presentation was found to be associated with survival. Factors correlating with decreased long-term survival included the persistence of *Pneumocystis* cysts 3 weeks after acute illness as well as the presence of marked interstitial edema on the lung biopsy specimen.

McCullough and Cole,¹¹ in a review of 62 patients, noted that if the alveolar-arterial oxygen gradient was greater than 60 mm Hg, 92% of the patients died during the acute event. Kales et al,¹² in a review of 145 patients, found several factors correlating with poor short-term survival. These included the degree of hypoxemia, the degree of hypocarbia (the lower the PCO_2 , the worse the prognosis), the elevation of lactate dehydrogenase levels, and hypoalbuminemia. In addition, the presence of additional pathogens worsened the prognosis.

Of our 18 children, 7 (39%) died during the acute PCP infection. Only 1 patient has survived longer than 27 months after PCP infection. Lactate dehydrogenase levels tend to be elevated in PCP,¹³ and did not distinguish survivors from nonsurvivors. The degree of hypoxia at presentation did not predict survival. In general, children with PCP do not present with mild disease with minimal hypoxia. All of our children had alveolar-arterial oxygen gradients of greater than 30 mm Hg. The absolute number of lymphocytes did not clearly distinguish survivors from nonsurvivors. While T4 cell counts tended to be

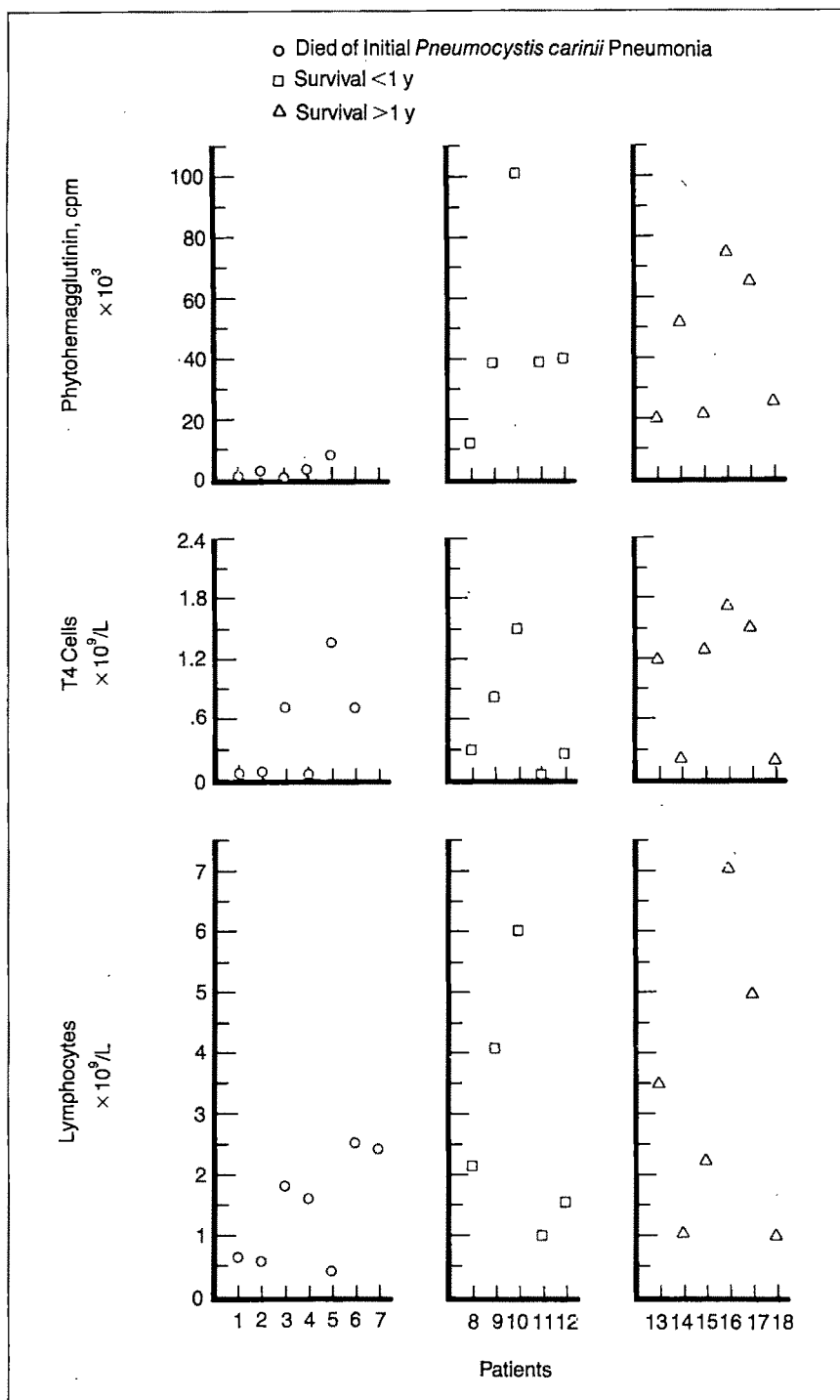


Fig 2.—Phytohemagglutinin responses, lymphocyte counts, and T4 cell counts in children with human immunodeficiency virus infection presenting with *Pneumocystis carinii* pneumonia. Patients were grouped by length of survival. Phytohemagglutinin responses were not obtained in patients 6 and 7; T4 cell count was not obtained in patient 7.

higher in patients surviving the longest, there was considerable overlap. No patient who survived an initial PCP attack had a markedly diminished PHA response, while the nonsurvivors had markedly diminished PHA responses.

Thus, the PHA response seemed to correlate best with short-term recovery from acute PCP.

Normal PHA responses in our laboratory are usually greater than 15 000 to 20 000 cpm or at least 50 times back-

ground counts. We consider a PHA response under 10 000 cpm to be significantly diminished. Similarly, ConA responses are usually 50 times background counts, and staphylococcal Cowan A and PWM are 20 times background counts. ConA responses did not predict survival as well as PHA, and ConA and PWM responses are diminished in most HIV-infected children, being the first immune abnormalities often seen.¹⁴

There have been several studies correlating immune status and clinical course in patients with HIV infection.¹⁵⁻¹⁷ In general, these studies demonstrated a higher incidence of opportunistic infection and poor outcome in patients with a diminished number of T4 cells and decreased lymphoproliferative responses both to mitogens and antigens. *Pneumocystis carinii* occurs in children both in the presence and absence of a normal PHA response. It appears that PHA response has more value in predicting survival from PCP in children, and not in identifying an at-risk group per se. It is not surprising that the patients with the poorest immune responses had the worst prognosis. However, there was no other specific clinical or laboratory finding at presentation that correlated as well as PHA response with survival from initial PCP. Mitogenic responses are not always available in acute situations. In our experience, it takes 3 to 4 days to obtain results. However, it does identify an at-risk population for fulminant PCP and early death. Identifying such a population is important in evaluating any future protocols regarding efficacy of PCP treatment or prophylaxis regimens.

As noted, in contrast to the adult studies, we saw no correlation between lactate dehydrogenase levels and survival. Albumin levels were lower in general in our older children, and levels of albumin were not predictive of survival. As we do not perform biopsies on children after therapy, we could not compare our data with those of Brenner et al.¹⁰ In fact, we rarely perform open lung biopsies at this point and rely initially on bronchoalveolar lavage.¹⁸

We cannot comment on the relative benefit of pentamidine vs trimethoprim/sulfamethoxazole, as others have.^{7,19}

Our use of anti-PCP drug therapy was not randomized and therefore no statement regarding the relative efficacy of each drug could be made. In the absence of a history of sulfa sensitivity, we routinely started our patients on a regimen of trimethoprim/sulfamethoxazole. In addition, the decision to switch from one drug to another, and the definition of "drug failure," was not always arrived at in the same manner in these patients. Pentamidine therapy tended to be initiated when the patient's condition was viewed as deteriorating with trimethoprim/sulfamethoxazole therapy, and this was often a subjective and variable decision. It should be noted that we have seen a significant incidence of adverse reactions to trimethoprim/sulfamethoxazole. Six children developed toxicity. Four had dermatitis, and two had bone marrow depression. While we prefer to maintain patients with prophylaxis therapy after PCP, trimethoprim/sulfamethoxazole therapy obviously had limitations.

The coexistence of other infections is important. Two of the seven patients who died were known to have disseminated MAI before presenting with *Pneumocystis*. One additional child was found to have disseminated cytomegalovirus infection at postmortem examination.

In two other children, premortem blood cultures subsequently yielded MAI after death. In one of these latter two children, blood cultures obtained shortly before death also yielded *C albicans*. This child was hospitalized for several weeks with multiple central lines. Of the initial survivors, one child was diagnosed with cytomegalovirus retinitis 2 months later, and five others subsequently developed MAI several months later. We feel that diminished immune status correlates with a higher risk for presentation with multiple opportunistic infections as well as early death from PCP. While five of seven children dying of acute PCP had an additional opportunistic infection, in only two was this clinically apparent before death; it would not be used as a predictor for PCP survival.

Our one surviving patient is of obvious interest. None of his laboratory data separate him from the other children who survived the initial PCP infection. He did go on to develop pulmonary lymphoid hyperplasia, which was confirmed histologically 1 year after PCP infection. Pulmonary lymphoid hyperplasia is an entity involving hyperplasia of the bronchial-associated lymphoid tissue.^{3,20}

It is not clearly associated with any pathogen, although Epstein-Barr virus has been implicated. He is the only one of our patients with PCP who subsequently developed pulmonary lymphoid hyperplasia. He has done well while receiving trimethoprim/sulfamethoxazole prophylaxis therapy, although he has required steroid therapy for his pulmonary lymphoid hyperplasia.²¹ There were no sequelae to his course of corticosteroids.

CONCLUSION

Children with PCP have a high incidence of mortality (39%) with their first attack. The prognosis for patients who survive the initial attack is extremely poor, with an overall mortality of greater than 90%. Thus, this group of children with HIV-1 infection clearly might benefit from more aggressive therapy for HIV-1 infection with agents such as zidovudine when they become available. To prevent the occurrence and recurrence of PCP, the use of prophylactic therapy in these high-risk children also needs to be evaluated.

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Pyomyositis in a Child With Acquired Immunodeficiency Syndrome

Patient Report and Brief Review

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• Although common in tropical regions, pyomyositis is rare in the continental United States. Fewer than 50 cases have been reported to date. It is characterized by suppurative of large muscle groups that can, if not quickly and appropriately treated, lead to sepsis and death. Diagnosis can be difficult secondary to the atypical appearance of the abscess process early on. Almost all cases have occurred in otherwise healthy people. The simultaneous occurrence of pyomyositis and immunodeficiency is rare. A recent report of a case in an adult with the acquired immunodeficiency syndrome (AIDS) is not, however, unexpected. We describe the first documented occurrence of pyomyositis in a child with AIDS. A brief review of the topic is included. Pyomyositis should be included in the list of unusual infections that can occur in children with AIDS.

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Pyomyositis (spontaneous bacterial myositis, tropical and nontropical myositis, and primary suppurative myositis) is a suppurative bacterial infection of skeletal muscle usually caused by *Staphylococcus aureus*.¹ First described more than 130 years ago,² it is very common in tropical regions but rare in temperate climates.³ Since 1971, fewer than 50 cases have been reported in the continental United States.⁴ A pre-

dominance of healthy young males is noted.^{1,5} The youngest described patient is a 3-week-old neonate.⁶ A recent report describing this illness in an adult with the acquired immunodeficiency syndrome (AIDS)⁴ prompted this brief review of the topic and the first reported case of pyomyositis in a child with AIDS.

PATIENT REPORT

The patient, a 3½-month-old black male infant, was well until age 1 month, when hepatosplenomegaly, jaundice, and thrush were noted. Results of anti-human immunodeficiency virus (HIV) antibody tests (enzyme immunoassay with confirmatory Western blot) were positive in both the patient and his mother. The mother denied parental substance abuse and a history of blood product transfusion. She was, however, the sexual partner of an intravenous drug abuser who tested positive for anti-HIV antibodies. Additionally, the patient's serum was positive for HIV p24 antigen (Abbott Laboratories, North Chicago, Ill). The hepatosplenomegaly and jaundice were thought to be secondary to HIV infection. He was discharged with a diagnosis of perinatally acquired symptomatic HIV infection (AIDS).

Persistent fever and diarrhea developed. At age 3 months he was readmitted to the hospital. A swelling on the back had been noted 5 to 7 days prior to hospitalization. The physical examination revealed a small, undernourished, sickly appearing male infant in no acute distress. His height and weight were below the third percentile and his temperature was 37.6°C (axillary). Both heart and respiratory rates were increased (152 beats per minute and 42 breaths per minute, respectively). A small abscess was noted on the left eyelid. The tympanic membranes, heart, and lung were normal. Generalized lymphadenopathy was present. Liver and spleen enlargement and thrush were again

documented. A *Candida*-like rash involved the perineum. Neurologic examination results were abnormal. It was questionable whether the patient could follow light and respond to loud noises. Spontaneous nystagmus of the left eye was noted.

A 3 × 2-cm paraspinal mass lesion was found on the lower back to the left of the midline. The overlying skin was neither inflamed nor warm. There was no evidence of dermal suppuration. The lesion was firm, nontender, and barely noticeable while the patient was at rest; it became quite prominent, however, during crying or straining.

Results of laboratory studies showed an elevated total white blood cell count of $14.7 \times 10^9/L$ with 0.55 polymorphonuclear cells, 0.23 band forms, 0.17 lymphocytes, 0.03 mononuclear cells, 0.01 myelocytes, and 0.01 metamyelocytes. Marked anemia was present (hemoglobin, 79 g/L; hematocrit, 0.24). Lumbar puncture revealed $18 \times 10^6/L$ white blood cells and $1800 \times 10^6/L$ red blood cells. There were 0.51 polymorphonuclear cells, 0.37 lymphocytes, 0.10 band forms, and 0.02 mononuclear cells. Protein and sugar levels were normal. Gram's stain was negative. Moderate elevation of liver enzyme levels was noted: γ -glutamyl transferase, 230 U/L; alanine aminotransferase, 384 U/L; and lactate dehydrogenase, 1296 U/L. A chest roentgenogram showed an enlarged heart, interstitial infiltrates, and a small pleural effusion. The patient began to experience fevers to 39°C. Several physicians felt that the lack of erythema and warmth suggested the lesion was probably not an abscess. Nonetheless, intravenous antibiotic therapy (ceftriaxone) was initiated.

An ultrasound examination revealed a nonpulsatile paraspinal mass that was not cystic, did not contain fluid and/or air, and did not communicate with the spinal canal or retroperitoneum. The mass was deep to the fascia and when it was incised, yellow, nonfoul smelling, thick, purulent material was obtained. Loculated areas were disrupted

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Reprints not available.

and the wound was irrigated and packed. Fifty milliliters of pus was evacuated. Gram's stain revealed very few gram-positive cocci in clusters.

Cultures of the abscess yielded penicillin-resistant *S aureus*. Ceftriaxone therapy was discontinued and intravenous sodium nafcillin therapy initiated. All other cultures, including blood, remained negative. The patient remained irritable and fed poorly. On the eighth hospital day, oral antibiotic therapy (cephalexin) was started. He was sent home several days later.

Two days after discharge, he was readmitted to the hospital. Elevated fibrin split products, low platelet count, and prolonged partial thromboplastin and prothrombin times were found. These findings were thought to be compatible with either disseminated intravascular coagulation and/or liver dysfunction, possibly secondary to hepatitis caused by HIV infection. The total white blood cell count on admission was $13.0 \times 10^9/L$ with 0.54 polymorphonuclear cells, 0.11 band forms, 0.34 lymphocytes, and 0.01 mononuclear cells. The patient had an acute pulmonary hemorrhage and died shortly thereafter. Permission for autopsy was denied. Cultures of blood, spinal fluid, and abscess cavity, taken on admission and prior to parenteral antibiotic therapy, yielded no organisms.

COMMENT

As stated above, pyomyositis is rare in the continental United States but is almost endemic in tropical regions. In Uganda, for example, it has accounted for almost 4% of all admissions to the surgical service of a large city hospital.⁷ Interestingly, many of the cases in the United States occur in areas that are characterized by high temperature and humidity.^{8,9} Clinically, there are no major differences between tropical and nontropical forms.

Many theories have been proposed to explain the discordance of geographic incidence and why muscle tissue, which is normally resistant to infection,⁹ can be affected in so isolated a way. These theories include (1) the possibility of concomitant parasitic¹⁰ or viral^{11,12} muscle infestation, which could lead to muscle fiber destruction and subsequent secondary bacterial infection; (2) nutritional imbalances^{13,14} leading to diminished host immune responsiveness; and (3) the role of preceding trauma to muscle tissue.¹⁵

The first two have not conclusively been shown to play a role, but there is evidence, from both laboratory animal²

and human clinical studies,¹⁶⁻¹⁸ that suggests that preceding trauma or interruption of vascular supply to muscle may be predisposing factors. The occurrence of a large number of cases in well-nourished and healthy citizens of the Hawaiian islands¹⁹ appears to diminish the role of poor nutrition and parasitic infestation as contributing factors. However, as study of the same series of patients suggests, preceding trauma and the occurrence of a concurrent and/or recent source of pyoderma may be significant. Perhaps transient bacteremia is also important, which might help explain the inability to document blood-borne infection in the vast majority of patients.³

A possible explanation for the tropical occurrence of this disease may be that people in these regions frequently walk shoeless and have a high incidence of repetitive minor foot trauma that may serve as loci for areas of "silent pyoderma"²⁰ that can lead to hematogenous spread.

A single muscle group is usually affected, but there may be multiple sites of involvement. The muscle groups most frequently involved include those of the thigh, buttocks, arm, lower leg, groin, chest wall, and shoulder, in decreasing order of frequency.¹ Approximately one third of patients have axial involvement.¹⁷

There are three stages of clinical progression.¹ The first is characterized by cramping pain and tenderness. Fever is not usually present. The illness progresses over 1 or 2 weeks with increasing edema, tenderness, and onset of fever. There may be a mild leukocytosis. The involved area feels indurated and has a "woody" quality. There is usually no evidence of fluctuance. As the untreated disease progresses into the second or suppurative stage, pain, tenderness, and edema intensify. Fever becomes prominent. Fluctuance occurs. Most patients seek treatment during this stage. The third stage is characterized by intense suppuration. The entire muscle may be replaced by pus. Septicemia and death may follow.

Diagnosis can be difficult. The disease may be mistaken for a variety of conditions, including muscle strain, hematoma, contusion, and soft-tissue sarcoma.²¹ This frequently occurs in the

early stages when there is little inflammation. Subsequent delay in therapy can be catastrophic. Muscle enzyme levels are rarely helpful in making the diagnosis.¹⁰

Localization of the purulent process has been aided by ultrasound,²² gallium scanning,²³ technetium Tc 99m bone scanning,²⁴ and computed tomography.²⁵ Technetium Tc 99m bone scanning is especially useful for detection of secondary silent sites.²⁶ Scanning techniques are also useful to rule out other conditions (such as vascular masses) that should be defined prior to surgery and to determine whether contiguous sites, such as bone, are involved.

The most commonly recovered organism, *S aureus*,³ is responsible for over 95% of cases. Most isolated organisms have been resistant to penicillin. The few cases caused by group A β -hemolytic streptococci appear to be more malignant and progressive.^{27,28} Recently, a case of toxic shock syndrome in association with pyomyositis has been described.²⁹

Therapy is relatively uncomplicated.¹ In the early stages, before large amounts of pus accumulate, many cases can be treated with intensive antibiotic therapy alone and will usually resolve in 2 to 3 weeks. For those who have entered the second stage of illness, surgical incision and drainage, in addition to antibiotic therapy (preferably a β -lactamase-resistant antistaphylococcal agent), is mandatory. If therapy is initiated quickly, complete resolution is the rule.

Our patient seems to have had a classic case of pyomyositis, which appears to have been diagnosed in the first stage of illness. A possible locus of infection was identified early (eyelid abscess). Unfortunately, this was not cultured. As noted, there was some question as to the nature of the mass. The classic occurrence of induration without redness or warmth, as is classically seen in pyomyositis, delayed the awareness that this was an abscess. If elevated, muscle enzyme levels might have suggested a diagnosis of myositis, but, as stated, results are almost always normal in patients with pyomyositis.

It is not surprising that this disease can be found in patients with evidence of immunodeficiency.⁴ Its occurrence in a

patient with transient hypogammaglobulinemia is documented.³⁰ Indeed, patients with pyomyositis have been described who have associated illnesses (diabetes mellitus,³¹ acute lymphocytic leukemia,³² Felty's syndrome,³³ and aplastic anemia³⁴) that can have immunodeficiency as part of their pathophysiology.

We cannot be sure that the death of this patient was not related to systemic bacterial infection. It would not be unexpected, however, that sepsis secondary to pyomyositis could be a cause of serious illness in young children with AIDS. The immunodeficiencies in these children^{35,36} make them particularly susceptible to infection with virulent pyogenic organisms.³⁷ The possible usefulness of prophylactic intravenous immunoglobulin therapy for bacterial infection in these patients comes to mind when presented with a case like this. Although the efficacy of such therapy is not definitively known, this child was being considered for entry into the national placebo-controlled double-blind study of such therapy.

Pyomyositis should be added to the list of those infrequent, but not necessarily opportunistic, bacterial infections that can cause increased morbidity and mortality in children with AIDS.

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In Other AMA Journals

ARCHIVES OF NEUROLOGY

Duchenne Muscular Dystrophy Manifesting Carriers

Paul E. Barkhaus, MD, James M. Gilchrist, MD (*Arch Neurol*. 1989;46:673-675)

Mucopolysaccharidosis I Presenting With Endocardial Fibroelastosis of Infancy

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• We describe two female infants with Hurler syndrome (mucopolysaccharidosis I) whose deaths are attributed to cardiac failure with associated, autopsy-confirmed endocardial fibroelastosis. One infant had confirmed α -L-iduronidase deficiency in cultured dermal fibroblasts, and the other infant had histologic evidence of tissue mucopolysaccharide accumulation at autopsy and a sibling with confirmed α -L-iduronidase deficiency and the Hurler syndrome phenotype. Clear cells ("Hurler" cells) were identified within the myocardium and endocardium of both infants. We propose that the ventricular mural accumulation of mucopolysaccharides induced extensive proliferation of elastic or collagen fibers within the endocardium. Cardiac failure may precede recognition of clinical and roentgenographic features of Hurler syndrome. Our findings and a literature review suggest that certain heritable storage disorders, including mucopolysaccharidosis I, should be considered when infants have clinical electrocardiographic and echocardiographic findings consistent with endocardial fibroelastosis or have autopsy-documented endocardial fibroelastosis.

(AJDC. 1989;143:782-784)

Endocardial fibroelastosis of infancy (EFE), characterized by a thickened noncompliant left ventricle, can be present or develop in a causally heterogeneous group of cardiac disorders. Previously, EFE has been pathogenetically attributed to viral infections, hereditary and nonhereditary congenital de-

velopmental defects in the endocardium, subendocardial hypoxia, and impaired lymphatic drainage of the heart.¹ Lurie² recently emphasized the concept of EFE as a reactive process set off in the endocardium by a stressed myocardium, as a result of a viral inflammatory process, obstructive defect of the left heart, genetic disorder, etc. We describe two infants with congestive heart failure and EFE as a presenting manifestation of mucopolysaccharidosis I (MPS I [Hurler syndrome]).

PATIENT REPORTS

PATIENT 1.—A female infant was the product of an uncomplicated term pregnancy and delivery to 26-year-old, nonconsanguineous white parents. Her birth weight was 3.5 kg; length, 49.5 cm; and head circumference, 33 cm. The family history was negative for birth defects, known heritable disorders, mental retardation, and heart disease of childhood onset. Growth and development during early infancy were normal. At age 4 months she was hospitalized with a 2-week history of poor feeding, increased sweating, and labored breathing. Physical examination revealed a head circumference of 42.3 cm (90%), slight frontal bossing, synophrys, and a high-arched palate. Her respiratory rate was 48/min without subcostal retractions or adventitious sounds. The heart rate was 180 beats per minute, and the point of maximal cardiac impulse was displaced to the left anterior axillary line. No cardiac murmur was auscultated. The liver was palpable 4 cm below the right costal margin with a span of 7 cm by percussion. The spleen tip was palpable at the level of the umbilicus. No extremity edema or limitation of joint mobility was present. Neuromuscular tone and deep tendon reflexes were normal.

Chest roentgenograms confirmed marked cardiomegaly. An electrocardiogram was significant for ST segment depression in leads II, III, and aVF and left-ventricular hypertrophy with strain as well as poor R-wave progression from the right to the mid-precordial leads. An echocardiogram was remarkable for severely reduced left-ventricular contractility and thickening of the left-ventricular wall and septum compatible with a cardiomyopathy. The mitral valve was also thickened. Viral cultures of the

throat and rectum were negative. Acute and convalescent serum complement fixation titers for enteroviruses, including coxsackievirus B, were negative. The patient was given oxygen, digitalis, and diuretics, resulting in marked clinical improvement.

Because of mild facial coarsening and marked splenomegaly, the diagnosis of a metabolic storage disease was entertained. Peripheral blood smear examination revealed numerous vacuoles in the cytoplasm of lymphocytes. Roentgenograms demonstrated anterior hypoplasia and beaking at L-2 and L-3, and slightly broadened phalanges. Slit-lamp examination confirmed mild corneal clouding bilaterally. Results of a urine mucopolysaccharide screen were positive for dermatan sulfate and heparan sulfate. Electron microscopy of skin revealed the presence of storage material. A skin fibroblast assay confirmed the absence of α -L-iduronidase activity compatible with MPS I.

By age 6 months the patient had mild hypotonia and mild thoracolumbar kyphosis. Her motor developmental index was 92 and her performance developmental index was 86 on the Bayley Scales of Infant Development.

At age 9 months the patient died of severe congestive heart failure precipitated by an upper respiratory tract infection.

At autopsy the most striking findings were noted in the heart, which was markedly enlarged at 95 g (normal, 41 ± 5 g), with a diffusely pale, glistening appearance. The mural endocardium of all chambers was diffusely thickened up to 0.1 cm, most prominently within the left ventricle, and especially the membranous portion of the ventricular septum and chordae tendinae. There was thickening of the mitral and aortic valve leaflets without evidence of stenosis. Severe luminal narrowing up to 70% was present focally within all three major coronary arteries. Histologically, the myocardium showed mild hypertrophy, with numerous collections of clear ("Hurler") cells in the interstitium between myocardial fibers. These clear cells stained with alcian blue (pH 2.5), periodic acid-Schiff, and toluidine blue. The endocardial and epicardial thickenings were composed of proliferations of fibroelastic tissue, confirmed by elastic stains. Few clear cells could be demonstrated by special stains within the fibroelastic proliferations, and they were noted predominantly adjacent to the myocardium. The coronary artery narrowing and the valvular thickenings were due to

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The opinions and assertions contained herein are the views of the authors and are not to be construed as official or as reflecting the views of the US Department of the Army or the Department of Defense.

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accumulations of clear cells and collagen.

Other autopsy findings included hepatomegaly (410 g; normal, 288 ± 67 g) and splenomegaly (41 g; normal, 18 ± 5 g). Varying numbers of clear cells were identified with special stains in most organs, most prominently in the liver sinusoids, renal interstitium, thymus, lungs, and lymph nodes. There was prominent vacuolization of hepatocytes. Permission for postmortem examination of the central nervous system was denied.

PATIENT 2.—The first girl born to a non-consanguineous, healthy couple was the product of a term, uncomplicated pregnancy and delivery. Her birth weight was 3.8 kg and her birth length was 51 cm. An incomplete cleft of the hard palate and left talipes equinovarus were present. She was an irritable infant who had recurrent upper respiratory tract infections. At age 5 months her motor development was mildly delayed. At age 8 months her head circumference was 46 cm (>95%), with a large anterior fontanelle measuring 4×5 cm. A respiratory illness developed at age 8 months, and she was subsequently found dead in her crib. A postmortem examination established the presence of EFE.

The family's second daughter was physically and developmentally normal. The third daughter was referred at age 1 year for genetic evaluation because of global developmental retardation. She was the product of an uncomplicated term pregnancy, her birth weight was 3.7 kg, and her length was 51 cm. The parents noted a striking resemblance in the child's early infancy to their first child, who had died of EFE. Physical examination at age 12 months revealed a flat nasal root, facial coarsening, bilateral corneal clouding, and hepatosplenomegaly. Results of cardiac examination were normal.

Roentgenograms revealed inferior beaking of L-2 and L-3 anteriorly and broadened metacarpals and phalanges. Urine mucopolysaccharide excretion was elevated at 90 cetyl pyridinium chloride units per millimole of creatinine by the alcian blue method. A white blood cell α -L-iduronidase assay revealed an almost complete deficiency (0.007 U per gram of protein). Her most recent evaluation at age 4 years revealed a typical Hurler syndrome phenotype, with short stature (94 cm). Echocardiography revealed thickening of the aortic and mitral valves, but endocardial thickening was not noted.

Review of the autopsy of the first sibling was significant for marked cardiomegaly (89.6 g). The left ventricle was globular, and there was marked dilatation of the left ventricle, right atrium, and right ventricle, with mild left-atrial dilatation. The salient feature on gross pathologic examination was striking pallor of the thickened endocardium of the left ventricle and right ventricle, most pronounced near the base of the aortic valves

and the base of the pulmonary valves, respectively. Microscopically, the endocardial thickening consisted primarily of collagenous fibers and reticular tissue. There was no significant elastic tissue with special stains. The endocardium stained mildly metachromatic with toluidine blue and showed scattered cells with fine vacuolization of enlarged cytoplasm. The myocardial cells showed no vacuolization, but there was some separation of myocardial fibers by clear cells in the interstitium adjacent to the endocardium. The aortic cusps were slightly thickened, and there was fine pebbling of the endothelial lining of the ascending aorta. There was marked intimal thickening of the coronary arteries, with 60% stenosis, consisting largely of fibrous tissue and clear cells, with destruction of the internal elastic lamina.

Other autopsy findings included hepatomegaly (310 g; normal, 277 g) with fine vacuolar changes in the parenchymal cytoplasm and periodic acid-Schiff-positive material that was present primarily in the Kupffer cells, splenomegaly (32 g; normal, 20 to 25 g), flocculent material in Bowman's space in the kidneys, and pulmonary edema with a few areas of focal alveolar collapse. Sections of the spleen and central nervous system were not available. The brain was enlarged (935 g; normal, 714 to 852 g). Bacterial cultures of the blood, cerebrospinal fluid, and both lungs were negative. *Klebsiella pneumoniae* grew from a tracheal culture. Viral cultures of the heart and right lung were negative.

COMMENT

These two female infants with EFE were affected by an underlying mucopolysaccharide storage disorder, MPS I. Although the diagnosis was biochemically proved only in patient 1, the phenotype of patient 2, the characteristic pathologic changes, and biochemically proved MPS I in a full sibling almost certainly make this the primary diagnosis in patient 2 as well.

Although past epidemiologic data for EFE indicated an incidence of 1 in 5000 to 6000 live births,³ its incidence in North America has decreased in recent years.⁴ Its clinical presentation features the rapid onset of low-output cardiac failure in early infancy, often precipitated by an upper respiratory tract infection. Neither the clinical^{1,5} nor echocardiographic^{1,6} findings of EFE are pathognomonic, and its presence is confirmed by endomyocardial biopsy procedure or at autopsy. Microscopically, the fundamental pathologic change is the thickened endocardium, composed principally of elastic and collagenous fibers.⁷

Endocardial fibroelastosis is causally

heterogeneous; its etiologic and pathogenetic considerations and natural history have been extensively reviewed.^{2,5,8,9} Serologic and cultural evidence of extrauterine or intrauterine viral infection has strongly implicated coxsackievirus B myocarditis^{1,10-12} and, less commonly, other viruses.

Although most cases of EFE occur sporadically, familial occurrence of EFE has been documented, including parental consanguinity^{13,14} and concordance in monozygotic twins.¹⁵⁻¹⁷ Various patterns of inheritance have been proposed for familial cases, including autosomal recessive,¹⁸⁻²⁰ X-linked recessive,^{21,22} and incompletely penetrant autosomal dominant.^{22,23} The reported familial incidence of EFE in siblings has ranged from 4.0% to 19.0%.^{22,24,25} After reviewing the family studies of Chen et al,²⁴ Opitz⁸ suggested that, once cases presumed to have been induced by viruses are discounted, the empiric recurrence risk for the remaining cases may approach the 25% segregation ratio expected for an autosomal recessive trait.

This familial occurrence of EFE suggests the possibility of a genetically transmitted abnormality affecting myocardial metabolism. Glycogen storage disease type IIa and associated EFE have been previously reported in siblings,^{26,27} with biochemical and autopsy confirmation of their association.²⁷ In any case of EFE or familial cardiomyopathy, treatable entities, such as systemic carnitine deficiency, must be sought.²⁸⁻³⁰ Autopsy-confirmed EFE has been reported in two infants with Niemann-Pick disease type A^{31,32} and in GM-2 gangliosidosis (Sandhoff disease).³³ Neustein et al³⁴ reported severe biventricular EFE and abnormal mitochondria with X-linked recessive inheritance.

In view of the sudden early onset of cardiac failure of the patients described in this report, we propose that MPS I should be considered among the differential causes of EFE of infancy. Two previously described 4½-month-old infants who were facially normal and who died with clinical manifestations associated with EFE had autopsy findings of enlarged vacuolated cells in the heart, liver, lymphatic tissue, and spleen, which are compatible with MPS.^{35,36} The infant described by Strauss and Platt³⁵ had a thickened endocardium consisting of abundant elastic and collagenous fi-

bers, between which were embedded vacuolated cells. These pathologic findings are present in patient 1 in the present report. The endocardium of the infant described by Lindsay³⁶ was thickened, with abundant swollen vacuolated collagenous fibers; this is histologically similar to our review of the pathologic findings of patient 2 in the present report. Fong et al³⁷ reported EFE in infant siblings with MPS VI (Maroteaux-Lamy) who presented with cardiac failure.

Mucopolysaccharidosis I is due to a genetic deficiency of α -L-iduronidase, a specific lysosomal hydrolase responsible for the normal degradation of acid mucopolysaccharides. Intracellular accumulation of acid mucopolysaccharides and glycolipids develop in various tissues, and patients have excessive urinary excretion of dermatan and heparan sulfates. Dermatan sulfate normally plays a role in the extracellular organization of collagen, and an excess of dermatan sulfate in MPS I may induce abnormally extensive collagen deposition at inappropriate sites.³⁸ The cardiovascular pathologic findings of MPS I³⁹ are characterized by accumulation of clear cells, granular cells, and collagen bundles, with resultant diffuse thickening of various regions of the cardiac substructure, including the valve leaflets and annuli, chordae tendinae, and the membranous portions of the ventricular septum, endocardium, epicardium, and coronary artery intima. Hypertrophy of the myocardium, with clear cells present in the interstitium, and focal infiltration of the sinoatrial and atrioventricular nodes by fibroelastic tissue may also occur. We propose that mucopolysaccharide deposition was responsible for myocardial malfunction and stress, with the proliferation of collagen and/or elastic fibers within the endocardium of the hearts of these two infants, contributing to their sudden decline of cardiac function. Increased ventricular wall tension secondary to acid mucopolysaccharide accumulation within the myocardium may contribute to the process of endocardial thickening. Renteria et al³⁹ noted thickening of the mural endocardium from proliferation of elastic and collagenous fibrils in necropsy studies of five older children with MPS I. Some degree of endocardial fibroelastosis was noted as an incidental finding in various forms of MPS in one fifth of 68

autopsies that included cardiovascular pathologic examination.⁴⁰

We do not know how frequently MPS I initially clinically presents with low-output cardiac failure during infancy rather than the more widely recognizable facial coarsening, skeletal changes, corneal clouding, and developmental delay. However, the evaluation of even an isolated case with clinical and/or autopsy findings compatible with EFE during infancy warrants consideration of a growing list of metabolic disorders. These include MPS I and VI, carnitine deficiency, glycogen storage disease type II, Niemann-Pick disease, Sandhoff disease, and, potentially, others.

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Beware of Overtreating Children!

Allan S. Cunningham, MD

Some years ago I witnessed a clinical catastrophe involving a 4-year-old boy. A history of headaches led to skull roentgenograms that disclosed a large pituitary fossa. This triggered a series of clinical decisions that were climaxed by a carotid hemorrhage during transphenoid biopsy. Autopsy revealed an empty sella and a benign lymphangioma in adjacent bone. The case was a source of fascination and much earnest and perplexed discussion. The consultants had little experience with similar cases and it was not entirely clear who was in charge. The cause of the headaches in this otherwise-normal boy was never known, and the long-range outlook without intervention was strictly speculative. However, it was an avoidable catastrophe and the case sensitized me to the factors that cause overtreatment of children. Four recent journal articles have crystallized some random thoughts about this problem.

1. Stickler¹ discussed two infants who underwent unnecessary surgery that completed a chain of clinical decisions beginning with the naive use of growth charts.

2. The *British Medical Journal*² summarized the terrible repercussions of an epidemic of false sexual abuse that resulted when two inexperienced physicians overinterpreted a single physical sign known as reflex anal dilatation.

3. Sepkowitz³ chronicled the stagger-

ing increase in the rate of newborn intubation at one community hospital following the publication of unsupported guidelines for the management of meconium staining.

4. Kemper⁴ documented the large number of children hospitalized unnecessarily.

These articles will strike a chord in pediatricians who have broad experience, and they need to be read in detail. For our purposes the articles serve as a suitable introduction to the subject of overtreatment in children.

THE CASCADE EFFECT

There is a natural medical bias for "doing," and medical educators place great emphasis on early diagnosis and treatment. This emphasis is proper, but few experienced clinicians would deny that it has unwholesome side effects that produce a professional attitude toward patients that is a blend of altruism and fear. It leads to what one observer has called a "solemn commitment to the principle that the patient is sick until proved well,"⁵ and it has caused much mischief by way of frivolous testing, treatment, consulting, and hospitalization. The mischief occurs because, once begun, the investigative process is hard to stop, a reality that has been dubbed "the cascade effect."⁶

The term *cascade* refers to a process that proceeds stepwise but inevitably to its conclusion. The coagulation cascade and the complement cascade are familiar examples, but the effect occurs in larger biological systems such as the decision-making processes of medical groups. The momentum of the cascade effect in clinical decisions is the result of

several factors that is aptly summarized by *DICE*, a recently coined acronym.⁷

D stands for "diffusion of responsibility." The physician's sense of responsibility for therapeutic catastrophe declines in proportion to the number of consultants on a case. It can occur in any medical environment. Schoolman⁸ observed that clinical decision making in teaching hospitals

evolves through a series of subspecialists who provide an environment in which the diffusion of responsibility for decision making is tolerated, if not promoted. This environment permits the physician to deal with his discomfort by an acceptable procedure of allowing decisions to be made by others. When this procedure assumes multiple dimensions, the result is that no one is responsible for the patient. Decisions are made not by a patient advocate, but rather by a therapeutic advocate.

Balint⁹ has termed this phenomenon "the collusion of anonymity." In the boy whose case I used as my first example, seven different medical and surgical specialists had been consulted and it was not clear who was directing his care. Sometimes responsibility is surrendered to outside experts whose "guidelines" are used to make clinical decisions. The effect of guidelines or "standards of practice" is not always salutary, as emphasized in Sepkowitz's report.

I stands for "inexperience." We are more likely to initiate a clinical cascade with tests or procedures that we trust, and we tend to be more trusting at the beginning of our professional careers. Moreover, as experience increases clinicians tolerate wider deviations from normal in their patients and are less

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likely to initiate an unnecessary search for a pathologic lesion. Experience relates to persons, problems, and procedures. How well does the physician know the child? Is this the first clinical encounter? If the physician is a consultant, has he or she talked to the parents himself or herself, or has the history been obtained at face value from the patient's medical record? How many times before has the physician seen similar clinical problems? For an established diagnosis, is there a grasp of the condition's natural history? Is the clinician's general experience broad enough to recognize that the problem is outside his or her narrow expertise? If a procedure is involved, has he or she performed it before? For diagnostic procedures, is the technology standardized well enough to establish the range of normal or the effects of age? These questions are not merely rhetorical, and they apply to attending physicians as well as trainees. The physician primarily responsible for the false epidemic of sexual abuse had been in practice for less than 1 year,² and the decisions to operate on Stickler's^{1,10} patients rested heavily on data obtained from a poorly standardized procedure.

C stands for "cookbook thinking." Its first element is a tendency to make artificially sharp distinctions between normal and abnormal. Thus, the infant at the fifth percentile is considered sickly, simply because he is 2 SDs below the mean for height or weight, thereby initiating the cascade observed by Stickler.¹ A second element is the tendency to assume that all deviations from normal are related and to confuse simple association with causality. Thus, Sepkowitz⁸ report reveals that meconium is believed to be a cause of respiratory distress rather than a marker. This leads to a second error, which is a tendency to overlook the risks of intubation.^{11,12} The erroneous diagnosis of sexual abuse resulted from inadequate knowledge of the normal anus. The result was a social catastrophe.² Cookbooks are useful and they are necessary, particularly in bona fide emergencies. But recipes have subtleties that cannot be written down. The best cooks—and the best physicians—appreciate this.

E stands for "economics." Professional competition is intense. When incen-

tives are offered for performing tests or administering treatments regardless of outcome, and when status is increased by filling hospital beds, clinical perceptions change and there is an additional impulse toward treatment. This is particularly true when the physician's sense of personal responsibility is blunted and when he or she is insecure. By validating or invalidating certain clinical practices, good research can retard this impulse, although the economic incentives are sometimes too strong to permit valid trials. One doubts that economic incentives in the preceding cases were strong or direct, but they do not have to be.

Physicians today are accused of being "too scientific." It is one way patients have of complaining about impersonal care. But the criticism is misplaced. It is not science but technology that is the likely culprit. It is science—in the best sense—that will improve the *personal* quality of care by allowing us to choose truly helpful technology, use it appropriately, and discard what is useless or harmful.¹³

There is one other contributor to the cascade effect. This is *curiosity* or the *craving for certainty*.¹⁴ The fact that we cannot explain many of our patients' symptoms is a frustrating reality, and technology offers a kind of release in the form of a number, a tracing, or an image. Unfortunately, it also leads to artificial inflation in the amount of pathologic disorder harbored by a given population. Adolescents with chest pain or palpitations, for example, would be wise to keep quiet nowadays lest they initiate a series of examinations culminating in a diagnosis of "mitral valve prolapse." This is what the echocardiogram now finds in 35% of normal adolescents!¹⁵ The craving for certainty may have more sinister results if it leads to unnecessary lymph node biopsy and the erroneous diagnosis of malignancy.¹⁶ I do not suggest that chest pain or swollen glands be ignored. But the vast majority of these symptoms, and a host of other complaints, are self-limited. They teach us to exercise considerable restraint before we scratch the diagnostic itch.

We should acknowledge that disastrous and unnecessary clinical cascades are sometimes initiated by parents. Cir-

cumcision is a homely example. Routine circumcision of newborns is no longer recommended by most physicians and is done only if parents request it. Catastrophes are rare, but they do occur.¹⁷ Overuse of antibiotics is, in part, the result of parental pressure, with some regrettable results.¹⁸ I have seen parental cancer phobia and craving for certainty lead to unnecessary node biopsies and serious complications. Clinicians, of course, share responsibility for these misadventures, but the role of parental pressure in initiating an unfortunate chain of clinical events should not be ignored. Knowledge of the cascade effect and its trigger factors should help clinicians to resist such pressure.

THREE GOOD PHYSICIANS

There is another antidote to diagnostic and therapeutic excess. It is the patient who surprises us by recovering from serious illness (or what we thought was serious illness) with little or no treatment. Until we see such patients ourselves, we can learn from clinicians who have. I know of three outstanding examples.

Robert Bolande, MD, was the pediatric pathologist at my alma mater. His was a name I learned to recognize when I scanned the journals. In 1969 he published the report of an infant who recovered from disseminated neuroblastoma with no treatment whatsoever,¹⁹ and he wrote a series of articles pressing the point that malignant neoplasms in childhood are not always what they seem.²⁰

Eugene Blank, MD, was the pediatric radiologist during my residency. He had first been a pediatrician, and I remember his sympathy for sick children, as well as his warnings to the residents against overinterpreting "shadows on x-ray film." It was the heyday of aggressive pediatric urologic surgery, but he taught that reflux was largely a developmental phenomenon²¹ and that antireflux surgery was of dubious value. He was right²² and the lessons he taught carried over to other clinical areas, so that we learned to approach "abnormal" test results with skepticism and deliberation.

Ronald Illingworth, MD, has had a long and distinguished career in British pediatrics. He teaches that the first principle of pediatrics is "know the nor-

mal, or else . . ." and that its first corollary is the extraordinary range and variety in observations of healthy children.²³ His wide experience permitted a reserve of optimism, even for the most worrisome cases.²⁴

These clinicians and scholars, and others like them, remind us of the limits of medical knowledge and the virtues of patience and therapeutic restraint. Their observations are a tonic against clinical arrogance, anxiety, and haste.

COMMENT

We deal with elastic concepts and vague boundaries between normal and

abnormal, and it is too easy to allow nonclinical factors to intrude on clinical perceptions and decisions. In an era of marketing, competition, technological pressure, and overspecialization, physicians must remember they are primarily counselors, not technicians.²⁵ When consensus conferences assess clinical practices we must insist on honest science, not votes, as these practices legitimate support.²⁶ We are inundated by information and experts, but we cannot allow judgment to be warped by the craving for certainty. We need guidelines, but when "standards of practice" are legalistically imposed we must not

forget that it is individuals we care for and individuals who provide the care.

This is not a counsel of despair. Experienced clinicians can be found to solve most problems, and professional cooperation need not lead to diffused responsibility. Cookbook thinking is overcome by education and experience, and unwholesome economic factors are overcome by an altruistic spirit. I recognize that overtreatment is not the only problem in the medical care of children. However, in the present professional climate, I believe it is a serious problem that deserves emphasis and our attention.

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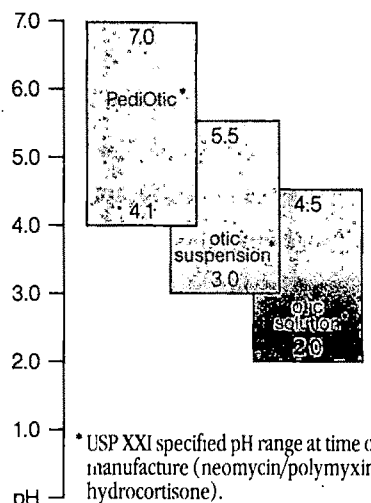
Francis M. Fesmire, MD; Robert F. Percy, MD; Robert L. Wares, MD; Terry L. MacMath, MD (*Arch Intern Med*. 1989;149:1294-1302)



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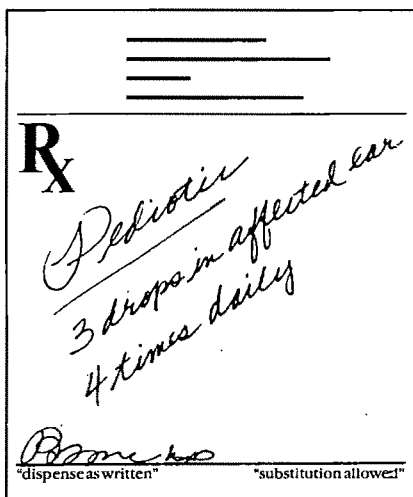
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REFERENCES: 1. Leyden JJ, Kilgman AM: Contact dermatitis to neomycin sulfate. *JAMA* 1979;242:1276-1278. 2. Prystowsky SD, Allen AM, Smith RW, et al: Allergic contact hypersensitivity to nickel, neomycin, ethylenediamine, and benzocaine. *Arch Dermatol* 1979;115:959-962.

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Urine Drug Screening in Mothers and Newborns

John D. Osterloh, MD, MS, Belle L. Lee, PharmD

• A retrospective analysis of comprehensive urine drug screening was performed during a 13-month period on specimens submitted from the Neonatal Nursery and Obstetrics/Gynecology wards at San Francisco (Calif) General Hospital (mothers, N=601; newborns, N=339). Of mothers and newborns, respectively, 19.2% and 15.3% of all admissions during this period were screened; 68.2% and 63.1% of urine samples submitted were positive for any drug; 38.8% and 21.1% of screens were positive for more than one drug; and 45.8% and 41.6% were positive for cocaine. In mother-newborn pairs (N=191) where urine samples were submitted within 4 days of each other, an 84% concordance was shown for cocaine and 67% for methadone, but concordance was much less for other drugs (<21%). These results indicate that cocaine was the most common drug detectable in the peripartum period and that both mothers and newborns should be tested to confirm the suspicion of drug effect or withdrawal in the newborn.

(AJDC. 1989;143:791-793)

The diagnosis of the effects of drug abuse on the newborn during the peripartum period depends on clinical signs and confirmation with urine drug testing in the newborn and mother. Though there is active investigation into the effects of drugs on the fetus and newborn,^{1,2} little is known about the types of drugs found in neonatal testing and about the concordance of drug detection in the mother and newborn. We conducted a retrospective survey of drug testing results from urine specimens submitted from obstetrics/gynecology and neonatal services in a large inner-city hospital to characterize the

types of drugs and concordance in mothers and newborns.

SUBJECTS AND METHODS

Urine drug screen results from the Neonatal Nursery and Obstetrics/Gynecology wards were compiled, covering a period of 13 months from April 1, 1987, through April 30, 1988. Drug screening was ordered by house staff for diagnostic purposes, to differentiate possible drug effect from signs caused by disease or pregnancy. Urine drug screens for mothers had been ordered on the basis of (1) a history of drug abuse, (2) signs and symptoms of drug use (track marks, skin abscesses, nasal mucosal ulceration), or (3) signs of pharmacologic effect (eg, elevated blood pressure due to cocaine vs pregnancy or disease). In the newborns, urine drug screens were ordered when there was (1) suspicion of drug effect (eg, opiate-induced respiratory depression or cocaine-induced irritability), (2) drug withdrawal (irritability, failure to feed, vascular instability, poor motor performance, wakefulness, tremulousness, hyperactivity, or hyperreflexia), or (3) a history of drug abuse or positive urine drug screen in the mother. Because specimens were submitted from both obstetric and gynecologic services, not all specimens were from mothers. The actual proportions of drug screens received from nonmother gynecologic patients is unknown. However, based on data after this study, the proportion appears to be less than 2%.

Urine samples were received by the San Francisco (Calif) Public Health Toxicology Laboratory at San Francisco General Hospital. Maternal urine samples were always screened by means of the following eight procedures: separate enzyme immunoassays for cocaine metabolite, opiates, and benzodiazepines (EMIT-Dau; Syva Company, Palo Alto, Calif); two chemical spot tests for salicylate and phenothiazines; thin-layer chromatography (Toxi-lab; Analytical Systems, Irvine, Calif) for 35 basic drugs including antidepressants, antihistamines, phenothiazines, narcotic analgesics, xanthines, amphetamines, and some sedatives; gas chromatography with flame ionization detection for alcohol; and gas chromatography with nitrogen-phosphorus detection, which will

detect or confirm a variety of drugs similar to that listed for thin-layer chromatography. In the newborns, the same procedures were applied except that the sensitivity of the gas chromatography procedure was severalfold less due to limited urine volume from the newborns (usually <10 mL). Approximately 80 different drugs of abuse and pharmaceuticals can be detected by these combined procedures. These methods allow detection of most drugs within 2 days of administration of recreational or therapeutic doses, except for alcohol, salicylate, and acetaminophen (detection interval, <1 day after dose).

The test results were compiled in two ways. Data from mothers and newborns were tabulated separately as to the number and types of drugs found. When a newborn urine specimen was received in the laboratory within 4 days of receiving the urine specimen from the mother, this was designated a mother-newborn pair. These were compiled as to types of drugs and agreement between findings in mothers and newborns.

RESULTS

A total of 940 urine drug screens were requested during this period. This represented 19.2% (601/3136) of obstetrics/gynecology admissions and 15.2% (339/2230) of neonatal admissions. Table 1 shows the occurrence of positive urine drug screens in mothers and newborns. There were 68.2% positive drug screens from the urine specimens submitted from mothers. Of the positive drug screens in mothers, 38.8% had more than one drug, with an average of 1.7 drugs per screen. For newborns, 63.1% were positive, with 21.1% having more than one drug. In both mothers and newborns (Table 2), the most prevalent drug detected was cocaine, present in 45.8% and 41.6% of all specimens, respectively. Cocaine was found as the only drug in 27.8% and 32.1% of the specimens submitted from mothers and newborns, respectively. An additional 29% of all maternal urine drug screens showed codeine, morphine, or methadone. These drugs were found with less-

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er frequency in newborns (8.8% of all newborns screened). In contrast, meperidine and lidocaine were found more frequently in the newborns, accounting for findings in 21.5% of all urine drug screens.

A total of 191 mother-newborn pairs were identified from the 940 urine samples submitted from obstetrics/gynecology and neonatal services during the 13-month period. Of the specimens, 15.3% were received on the same day, 38.4% on the next day, 29.4% within 2 days, 14.7% within 3 days, and 2.1% within 4 days. Therefore, 83.2% of the specimens were received within 2 days. No drugs were detected for both mother and newborn in 15.2% of the pairs, in 59.7% of the pairs the mother's and newborn's urine contained any one drug in common, and 25.1% of the pairs showed no agreement in the findings. Cocaine was found in either the mother or newborn in 113 pairs (59.2%), and there was agreement between mother and newborn for cocaine in 84% of the pairs (Table 2). When cocaine was not found in both mother and newborn, it was otherwise found in the mother. Codeine (41 pairs) was found more frequently in the mother (88%) than in the newborn (12%). This was also true for salicylates, acetaminophen, and benzodiazepines, which were less prevalent overall. Other drugs that were infrequently found in mothers and newborns included phen-cyclidine (5 mothers and 1 newborn), antihistamines (7 mothers and 2 newborns), antidepressants (4 mothers and 1 newborn), phenothiazines (6 mothers and no newborns), antiepileptics (3 mothers and 1 newborn), dextromethorphan (1 mother and 1 newborn), benzotropine (1 mother and no newborns), propoxyphene (2 mothers and no newborns), guaifenesin (1 mother and no newborns), trimethoprim (1 mother and no newborns), quinine (1 mother and no newborns), and a caffeine level of more than 20 mg/L (no mothers and 2 newborns).

COMMENT

Our survey of urine drug testing results in mothers and newborns demonstrated that the clinical suspicion of drug involvement may be confirmed in about two thirds of the cases when either the mother or the newborn is

Drug Screen Results	Mothers	Newborns
Total No. of drug screens	601	339
Positive screens, No. (% of total)	410 (68.2)	214 (63.1)
Average No. of drugs/screen	1.7	1.2
No. of screens with*		
≥4 drugs	34 (5.7/8.3)	4 (1.2/1.9)
3 drugs	34 (5.7/8.3)	9 (2.7/4.2)
2 drugs	91 (15.1/22.2)	32 (9.4/15.0)
1 drug	251 (41.8/61.2)	169 (49.9/78.9)

*Percentage of total screens/percentage of positive screens.

Drugs Found	No. (% of Total Screens)	
	Mothers (N = 601)	Newborns (N = 339)
Cocaine		
Positive cocaine screens	275 (45.8)	141 (41.6)
Cocaine alone	167 (27.8)	109 (32.2)
Cocaine with other drugs	108 (18.0)	32 (9.4)
Other drugs		
Meperidine	32 (5.3)	41 (12.1)
Lidocaine	41 (6.8)	32 (9.4)
Benzodiazepines	38 (6.3)	2 (0.6)
Salicylate and acetaminophen	60 (10.0)	1 (0.3)
Alcohol	12 (2.0)	1 (0.3)
Barbiturates	12 (2.0)	2 (0.6)
Codeine	75 (12.5)	5 (1.5)
Morphine	59 (9.8)	10 (2.9)
Methadone	40 (6.7)	15 (4.4)
Amphetamines	13 (2.2)	2 (0.6)

tested. From the mother-newborn pair data, evidence of drug presence was found in 84.8% of the pairs. Testing both mothers and newborns would appear to yield greater confirmation of clinical suspicion.

The finding that nearly two thirds of submitted urine samples were positive for at least one drug is not unusual when compared with findings from all specimens received at this hospital (66.9% positive). Cocaine is found in 25% of the drug screens submitted from this hospital (all wards), suggesting that the 45.8% found in mothers was due to a higher prevalence or a more aggressive selection of these patients. Cocaine was a common drug found in two small selective surveys in the newborn.⁸⁴ Recently, we performed a blinded prevalence study of cocaine in urine for mothers admitted for delivery and in newborns of these mothers (unpublished data,

1988). The prevalence of a urine sample positive for cocaine was 9% and 5% in mothers and newborns (N = 152 pairs during 1 month), respectively, in contrast to 46% and 42% in clinically requested testing demonstrated in this article. Hence, clinical selection of cases will result in a fivefold to eightfold greater yield in positive cocaine urine screens.

Only cocaine showed a high concordance between mother and newborn. Several factors may explain this finding. Cocaine as the parent compound will pass through the placenta and is likely to be found in the newborn.⁵ The early pharmacologic signs and symptoms due to cocaine (irritability and hyperactivity) may signal the clinician to obtain a urine sample for toxicologic screening while the drug is still present. Another factor may be a slower hydrolysis of cocaine to ecognine methyl ester

Table 3.—Drugs Found and Concordance in Mother-Newborn Pairs

Drug	Drug Present		
	In Mother and Newborn, No. (% Concordant)	In Mother, Not Newborn, No. (% Discordant)	In Newborn, Not Mother, No. (% Discordant)
Cocaine	95 (84)	16 (14)	2 (2)
Meperidine	7 (21)	9 (27)	17 (52)
Methadone	8 (67)	4 (33)	0 (0)
Morphine	4 (19)	10 (48)	7 (33)
Codeine	0 (0)	36 (88)	5 (12)
Lidocaine	4 (11)	16 (46)	15 (43)
Benzodiazepines	0 (0)	7 (88)	1 (12)
Salicylate and acetaminophen	1 (5)	21 (95)	0 (0)
Diphenhydramine	0	0	1
Chlorpheniramine	0	1	0
Antidepressants	0	0	0
Phenothiazines	0	0	0
Phenytoin	0	0	1
Amphetamines	2	1	0
Dextromethorphan	0	0	1
Alcohol	0	2	0
Benzotropine	0	0	0
Phencyclidine	0	0	0
Trimethoprim	0	0	1

by plasma and liver esterases.^{6,7} This may result in prolonged elimination of cocaine and its metabolite, benzoylecgonine.

Pharmacologic factors that would predispose toward finding drugs in mother and not in the newborn include higher concentrations of drugs achieved in maternal tissues and kidneys, poor drug penetration through the placenta, and earlier sample collection in the mother. Delayed withdrawal signs that result in late collection of urine, and consequent negative results of analysis, may be the most important explanation

for absence of detection in the newborn. In a small study of specimens received by a hospital laboratory, the majority of drug screens were considered to be obtained too late for adequate detection.⁸ The finding of a drug in the newborn, but not the mother, might be explained by a longer residence time in the infant due to less developed hepatic clearance, or possibly a relatively higher distribution into infant body water.⁹⁻¹² Obviously, medications given during labor and after urine specimen collection would not be detected in mothers, but may appear in the newborn.

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Of interest was the number of positive urine screens in newborns containing drugs that were likely to be administered to the mother while in the hospital. These included meperidine and acetaminophen as analgesics and lidocaine as a local anesthetic. The effects of these drugs on the newborn are not well studied, but meperidine is noted to cause neonatal respiratory depression when given more than 1 hour before delivery.¹³ Other narcotic analgesics (morphine, codeine, and methadone) were also frequently found, though some of these are probably related to drug abuse as well as medications. The prevalence of these drugs in toxicologic screens submitted from the entire hospital population is not dissimilar (8.8%, 7.1%, and 5.1%, respectively).

Many drugs were not found that otherwise might be expected because of the high prevalence of use. The rapid elimination of alcohol may explain its relative absence. Antihistamines, including antiemetics, could have been detected by the analytic methods used in this study, but few were found. Marijuana metabolite was not screened in this study, though it would further indicate the extent of drug abuse. In a large survey by interview, 9.5% of mothers reported using marijuana during pregnancy.¹⁴

This study suggests that cocaine is the most common drug found in the immediate peripartum period in this inner-city hospital. In addition, testing in both the mother and newborn should be attempted to improve diagnostic yield.

Paul Hu and David Fok are acknowledged for their assistance in the collation of laboratory reports.

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Non-Group A Streptococci in the Pharynx

Pathogens or Innocent Bystanders?

Gregory F. Hayden, MD; Thomas F. Murphy, MD; J. Owen Hendley, MD

• **Objective:** To determine whether β -hemolytic streptococci from groups other than A are an important cause of sporadic pharyngitis in children.

Design: Cross-sectional, case-referent survey.

Setting: General pediatric clinic at a military base in Ohio.

Participants: One hundred fifty children with symptomatic pharyngitis and 150 controls matched for age and time of presentation over a 20-month study period.

Interventions: None.

Measurements/Main Results: Anaerobic culture technique was used to improve isolation of β -hemolytic streptococci. Group A β -hemolytic streptococci were detected significantly more often among the ill children than among the controls (39% vs 16%, respectively). In contrast, non-group A β -hemolytic streptococci were isolated in similar frequency from the ill and control children (17% vs 21%, respectively). Non-group A β -hemolytic streptococci from groups B, C, F, and G were each isolated in similar frequency among the ill and control children. The isolation rate of non-group A organisms increased with age among both patients and controls.

Conclusions: Non-group A β -hemolytic streptococci seemed not to be an important cause of sporadic pharyngitis in this pediatric population.

(AJDC. 1989;143:794-797)

β -Hemolytic streptococci (BHS) from Lancefield group A are a well-recognized cause of pharyngitis in children.

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The views expressed herein are those of the authors and do not necessarily reflect the views of the US Air Force or the Department of Defense.

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Group A organisms can colonize the pharynx of asymptomatic children, but are isolated more commonly from children with pharyngitis than from healthy controls. Streptococci from Lancefield groups other than A have been associated with outbreaks of pharyngitis,¹⁻⁶ often with foodborne spread, but the role of these non-group A organisms in causing sporadic pharyngitis in children remains uncertain.⁶ Recent studies using anaerobic culture methods have demonstrated that BHS from groups other than A are frequently present in the pharynx of children with symptomatic pharyngitis, and further, that many such isolates of non-group A BHS will be missed if only the traditional aerobic method is used.⁷⁻¹²

The purpose of this article is to present the results of a study utilizing sensitive anaerobic culture methods to assess whether non-group A organisms were more common in the throats of children with sporadic pharyngitis than among carefully matched controls without pharyngitis.

PATIENTS AND METHODS

Population

One hundred fifty children with symptomatic pharyngitis who were seen by one of us (T.F.M.) at the Pediatric Clinic at Wright-Patterson AFB near Dayton, Ohio, were recruited for study during a 20-month period (February 1984 through October 1985). One hundred fifty children being seen at the same clinic for well care or a complaint unrelated to the respiratory tract who were matched to patients for age (within 1 year) and month of presentation were recruited to be controls and provided appropriate informed consent.

Clinical Evaluation

The clinical features of illness for each child with symptomatic pharyngitis were recorded on a standard, preprinted form. His-

torical items noted as being present or absent included fever, chills, sore throat, runny/stuffy nose, hoarseness or change in voice, headache, muscle aches, abdominal pain, vomiting, and diarrhea. On physical examination, the following features were noted as present or absent: tonsillar exudate, palatal petechiae, vesicles in the pharynx, tender cervical lymph nodes, otitis media, and exanthem.

Bacteriology

A throat culture was obtained from each patient and control by vigorously swabbing the posterior pharynx and tonsillar area with a rayon-tipped swab. Each swab was sent to the laboratory in modified Stuart's transport medium and inoculated within 6 hours onto a 5% sheep blood agar plate with an agar stab in the area streaked with the swab to highlight β -hemolysis beneath the surface of the agar. Following inoculation the plates were placed in an anaerobic environment (Anaerobic Gas Pak System, Baltimore Biologic Laboratory, Cockeysville, Md) and incubated at 35°C for 18 to 24 hours before reading. Plates showing no colonies with β -hemolysis were incubated in the anaerobic jar for an additional 24 hours before being discarded as negative. The Lancefield group of streptococci in β -hemolytic colonies was demonstrated using latex agglutination following enzymatic extraction of the group specific antigen (Streptex; Wellcome Diagnostics, Research Triangle Park, NC).

Statistical Analysis

Characteristics of the patients and controls were compared using χ^2 analysis or the Fisher Exact Test.

RESULTS

The 150 patients with pharyngitis were similar to the 150 controls in age (mean, 11.0 years in both groups), gender (41% and 49% males, respectively), and calendar month when sampled.

Group A BHS were isolated from the pharynx of 58 (39%) patients with pharyngitis and from 24 (16%) controls

Table 1.—Isolation Rate of β -Hemolytic Streptococci (BHS) by Lancefield Group From Throat Cultures From 150 Patients With Pharyngitis and 150 Controls

BHS Isolated	No. (%) of Patients With Pharyngitis*	No. (%) of Controls†	P‡
Group A	58 (39)	24 (16)	<.001
Non-group A (total)	25 (17)	32 (21)	
Group B	3 (2)	1 (1)	NS
Group C	7 (5)	12 (8)	
Group F	8 (5)	12 (8)	
Group G	8 (5)	8 (5)	

*Four children whose cultures contained streptococci belonging to two groups (A/F, A/F, A/F, and B/G) are counted in both groups.

†Three children whose cultures contained streptococci belonging to two groups (A/C, A/F, and F/G) are counted in both groups.

‡NS indicates not significant.

Table 2.—Clinical Features of Illness in Patients With Pharyngitis According to Throat Culture Result: β -Hemolytic Streptococci Isolated*

Clinical Feature	Group A (n=55)†	None (n=70)	Group Other Than A (n=22)†
Exanthem	15‡	1	0
Fever	76‡	46	32
Chills	34	21	18
Runny nose	53	56	57
Hoarseness	44	41	33
Headache	62	50	41
Muscle ache	20	9	23
Palatal petechiae	15‡	3	0
Exudate	26	27	18
Vesicles	4	1	0
Otitis media	7	6	0
Tender cervical lymph nodes	80‡	61	64
Vomiting	20‡	7	5
Abdominal pain	27	16	23
Diarrhea	4	3	5

*Percentages of patients with each clinical feature are shown.

†Three patients from whom β -hemolytic streptococci from both group A and another group were isolated are excluded.

‡ $P<.05$.

($P<.001$; Table 1). In contrast, BHS of groups other than A were isolated from 17% of patients and from 21% of controls ($P>.05$). The serogroups of the non-group A BHS in patients were also similar to those in controls. Group B BHS were detected in 1% to 2% and groups C, F, and G were present in 5% to 8% of both patients and controls (Table 1). The isolations of non-group A BHS were scattered throughout the 20-month study period. The numbers of children cultured each month varied according to our clinic schedule and illness patterns in the community, with little seasonal variation in the isolation rate of

non-group A BHS among the ill children.

Age was an important variable in the frequency of detection of BHS of both group A and groups other than A. The isolation rate of group A streptococci from both ill and well children was highest in the 5- to 9-year-old age group and declined with increasing age (Figure). In contrast, the isolation rate of non-group A organisms increased with age in patients and controls. Non-group A BHS were isolated from 7 (33%) of 21 controls 15 to 19 years old. The clinical signs and symptoms of illness in the 150 patients with pharyngitis were ana-

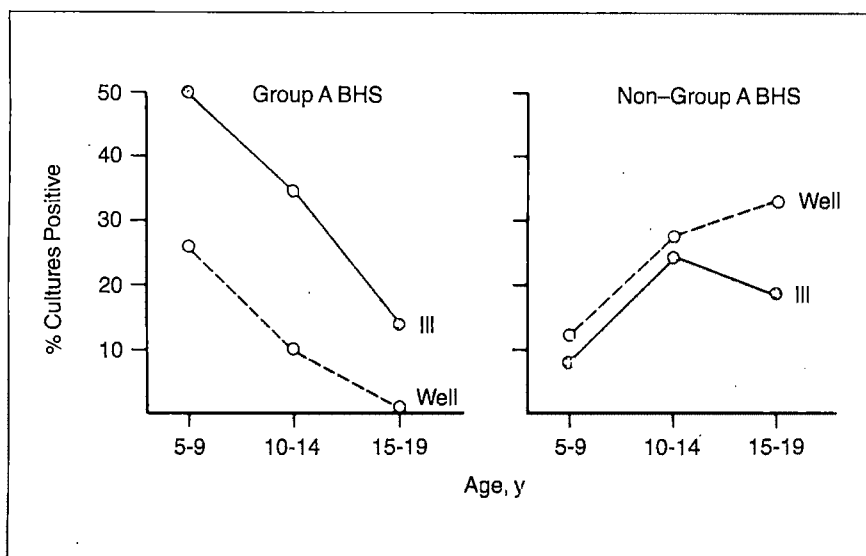
lyzed according to throat culture results. The 55 patients from whom group A BHS were isolated were more likely to manifest fever, vomiting, palatal petechiae, tender cervical lymphadenitis, and scarlatinaform rash than were the 70 patients from whom no BHS were isolated (Table 2, $P<.05$). In contrast, the clinical manifestations in patients with non-group A isolates were similar to those in patients with no BHS detected ($P>.05$). Patients with non-group A isolates were much less likely to have fever than were patients with group A isolates (32% vs 76%, $P<.05$), but the clinical characteristics of these two groups were otherwise not statistically significantly different ($P>.05$).

COMMENT

Detection of non-group A BHS in the throats of patients with pharyngitis is insufficient to prove a causative role in the illness. Such patients could be carriers of non-group A organisms with an illness caused by another agent, such as a respiratory virus. A higher prevalence (isolation rate) of non-group A BHS in throats of patients with pharyngitis than in controls without pharyngitis would suggest a causative role for non-group A BHS in sporadic pharyngitis. In this study, the prevalence of non-group A organisms detected with sensitive anaerobic incubation in patients with sporadic pharyngitis was essentially the same as the prevalence in age- and season-matched controls. This finding does not support the hypothesis that non-group A BHS play an important causative role in sporadic pharyngitis in children.

Much of the evidence suggesting that non-group A BHS cause pharyngitis has derived from reports of outbreaks of illness. For example, in one foodborne outbreak of pharyngitis,² group G BHS were isolated from 63% of a sample of ill conventioners and from only 2% of persons without pharyngitis. Hill et al⁴ described another foodborne outbreak in which group G BHS were isolated from the throats of 64% of college students with pharyngitis compared to 23% of randomly selected controls.

In contrast, most epidemiologic studies of sporadic pharyngitis have found little difference in prevalence of non-group A BHS in sick vs well persons.



Rates of isolation of group A (left) and non-group A (right) β -hemolytic streptococci (BHS) from the throats of ill and well children according to age group.

Hable et al,¹³ Glezen et al,¹⁴ Stewart and Moghadam,¹⁵ and McMillan et al,¹⁶ using standard aerobic incubation of culture plates, isolated non-group A BHS as often from healthy control children as from children with symptomatic pharyngitis. The Commission of Acute Respiratory Disease likewise observed no significant increase in the isolation rate of non-group A BHS from soldiers with acute respiratory disease compared with normal soldiers.¹⁷ Glezen et al,¹⁸ however, isolated non-group A organisms from 10.8% of university students admitted to the infirmary with pharyngitis and from only 0.2% of asymptomatic controls. Likewise, Putto¹⁹ detected non-group A BHS among 21% of children with febrile exudative tonsillitis and among only 11% of 92 controls without pharyngitis.

In this study, the prevalence of non-group A BHS in the throat was markedly influenced by age (Figure), emphasizing the importance of matching for age in epidemiologic studies of non-group A BHS. The prevalence in adolescents, regardless of whether they were well or ill, was more than double the prevalence in grammar school children. This relationship between age and prevalence of non-group A BHS has been suggested in earlier work from university student health centers.^{20,21}

Regarding group A BHS, a serologic response to streptococcal extracellular

antigens is an accepted means of differentiating invasive infection from superficial colonization.²² Whether serologic testing can be used in similar fashion to confirm infection with non-group A BHS is less certain. Some patients with pharyngitis and a throat culture positive for non-group A BHS have been shown to respond serologically to streptococcal extracellular antigens in earlier studies.^{17,18,23-25} Some group C and G organisms produce streptolysin O that is antigenically similar to that produced by group A organisms,²⁶ so that a rise in antistreptolysin O titer may potentially be a useful indication of infection with these organisms. Benjamin and Perriello³ reported an outbreak of pharyngitis at a boarding school in which students who were culture-positive for group C BHS had higher antistreptolysin O titers than culture-negative students. However, culture-positive students had similar titers regardless of whether they were symptomatic or asymptomatic, and the titers did not rise during a 3-week period of observation.

After obtaining appropriate informed consent, we examined acute and convalescent serum specimens obtained from 67 children with symptomatic pharyngitis for antistreptolysin O and antidesoxyribonuclease B antibodies using standard microtitration methods (G.F.H. and J.O.H., unpublished data,

1983).^{27,28} The dilution increments tested were 1:60, 1:85, 1:120, 1:170, etc. A rise in titer of two dilution increments or greater from acute to convalescent serum was defined as evidence for a serologic response to infection. Nine (56%) of 16 children whose anaerobic culture contained group A BHS demonstrated a significant titer rise in either antistreptolysin O or antidesoxyribonuclease B antibodies. Only 1 (6%) of 18 patients with non-group A BHS showed a similar titer rise ($P < .01$). The 18 non-group A isolates included 3 from group B, 3 from group C, 7 from group F, 1 from group G, and 4 bacitracin-resistant BHS which were not grouped serologically. Difficulty arises in interpreting these apparently negative findings, however, because the extracellular products of many non-group A BHS either differ from those of group A organisms or are unknown.²⁹ The serologic tests that have proved useful in evaluating possible infection with group A BHS may be inappropriate for assessing infection with non-group A organisms. More definitive serologic documentation of infection with non-group A BHS must await identification of the cellular and extracellular products of these organisms with development of the relevant serologic assays.

A radioimmunoassay has been developed to detect antibodies to group C streptococcal carbohydrate, but the assay is not specific for acute infection with group C organisms.³⁰ Rises in antibody levels have been detected after asymptomatic carriage of group C BHS and after group A streptococcal pharyngitis. A recently developed enzyme-linked immunosorbent technique to detect antibodies to the group C and G carbohydrates seems to be more specific and may prove more useful.³¹⁻³²

A prompt clinical response to antimicrobial therapy would provide indirect evidence that non-group A BHS cause pharyngitis. In one previous study, antibiotic therapy seemed to reduce the duration and severity of pharyngitis in patients from whom group B organisms were isolated.³³ In another study, however, there was no clear-cut clinical response to penicillin among children with non-group A isolates.¹⁹ Whether antimicrobial therapy is useful in children with pharyngitis and non-group A BHS

on throat culture remains uncertain. Because the isolation rate of non-group A BHS increases with age, additional placebo-controlled treatment trials of patients with pharyngitis and non-group A BHS on culture should most logically be conducted among adolescents and young adults. Such trials will, it is hoped, provide a clearer answer as

to the advisability of antibiotic therapy.

CONCLUSION

Non-group A BHS were isolated as often from the throats of age- and season-matched controls as from children with sporadic, symptomatic pharyngitis. Evidence from localized outbreaks of pharyngitis, however, suggests that

these organisms can cause pharyngitis in some instances. Clarification of the role, if any, of non-group A BHS in causing nonepidemic pharyngitis in children will require further study of the cellular and extracellular antigens of these organisms along with documentation of children's serologic responses to apparent infection.

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In Other AMA Journals

ARCHIVES OF OPHTHALMOLOGY

At Last: A Standard Electroretinography Protocol

Michael F. Marmor, MD, Gerald A. Fishman, MD (*Arch Ophthalmol*. 1989;107:813-814)

Epidemiology of a Cluster of Henoch-Schönlein Purpura

Thomas A. Farley, MD; Sheila Gillespie, MSN; Madjid Rasoulpour, MD; Narda Tolentino, MSPH; James L. Hadler, MD, MPH; Eugene Hurwitz, MD

• We investigated a case cluster of Henoch-Schönlein purpura that occurred in Connecticut during the fall and winter of 1987-1988. In Hartford County, where the case finding was most complete, 16 children were identified with disease onset during the 7-month cluster period (incidence, 1.7 cases per 10 000 children per year) compared with only 3 children with disease onset during the preceding 7 months. The incidence in Hartford County was higher among urban (4.8/10 000) and Hispanic (8.6/10 000) children and children in lower socioeconomic groups (6.9/10 000) than among suburban children or children in higher socioeconomic or different racial groups (0.9 to 1.1 per 10 000). We performed a case-control study involving 14 of the 16 case children from Hartford County, 10 case children from nearby areas, and 47 control children matched to the case children by age and race. Case children were more likely than control children to have had a sore throat during the month before the onset of Henoch-Schönlein purpura (52% vs 22%; odds ratio, 3.8; 95% confidence interval, 1.1 to 13). This difference and other smaller differences between case and control children suggest that the cluster may have been caused by person-to-person spread of an infectious agent of the respiratory tract to susceptible hosts. To our knowledge this is the first report of a cluster of Henoch-Schönlein purpura, and it provides clues for a better understanding of the etiology and epidemiology of the disease.

(AJDC. 1989;143:798-803)

Henoch-Schönlein Purpura (HSP) is a syndrome of unknown etiology that primarily affects children.^{1,2} Henoch-Schönlein purpura typically presents as a raised purpuric rash most prominent on the buttocks and lower legs, usually associated with crampy abdominal pain, arthritis, and/or hematuria.² A small percentage of children with HSP experience serious complications, such as intussusception, gastrointestinal hemorrhage, or chronic glomerulonephritis.^{2,4}

Although HSP was first described in the early 1800s, little is known of its etiology or epidemiology. It is believed that HSP is caused by an IgA-mediated immune response to a variety of foreign antigens.^{5,7} Isolated case reports have suggested links to specific exposures, such as drugs or infections,^{8,12} but no causative agent is apparent in the vast majority of cases. Henoch-Schönlein purpura is not generally a reportable disease, and its incidence in the community is unknown. We know of no previous reports of clusters or epidemics of HSP.

In November 1987, the Connecticut Department of Health Services was notified of four Hispanic children seen with HSP at a single medical center over a 2-week period. Other cases identified by contacting area pediatricians suggested

the presence of a cluster in the city of Hartford and the surrounding county by the same name. We investigated this cluster and carried out a case-control study in an attempt to describe the basic epidemiology of the illness and identify risk factors associated with its occurrence.

METHODS

Descriptive Epidemiology

In Hartford County we identified cases of HSP in children by telephoning all pediatricians in primary care practice and pediatricians on the staff of all general hospitals. Physicians were called between December 1, 1987, and January 30, 1988, and were asked to report cases of HSP seen since January 1987 and to continue reporting new cases through the end of 1988. All pediatricians were again contacted by mail in August 1988 to encourage continued reporting. The data presented herein represent those cases reported as of September 15, 1988.

A case was defined as a child under age 15 years who had received a physician diagnosis of HSP and who had the following signs and symptoms: (1) a vasculitic or purpuric rash most prominent on the buttocks or lower legs and (2) hematuria, abdominal pain, or joint pain. The HSP onset day was defined as the day the first of these symptoms or signs was noted. Cluster-related cases were defined as those cases with HSP onset between August 1, 1987, and February 29, 1988.

Incidence rates per 10 000 children under age 15 years per year were calculated by various demographic features in Hartford County. Population estimates for children under age 15 years by race and census tract were taken from the 1980 census.

Since the cluster was not clearly confined to Hartford County, we also attempted to identify cases that occurred in 1987 and 1988 in the remainder of the state. In the other counties in Connecticut we sent letters requesting case reports to all pediatricians and family practitioners and telephoned pediatricians and family practitioners in all teaching

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hospitals. In addition, to provide a comparison with the city of Hartford, we telephoned all practicing primary care pediatricians in the cities of Bridgeport and New Haven, which are demographically similar to Hartford.

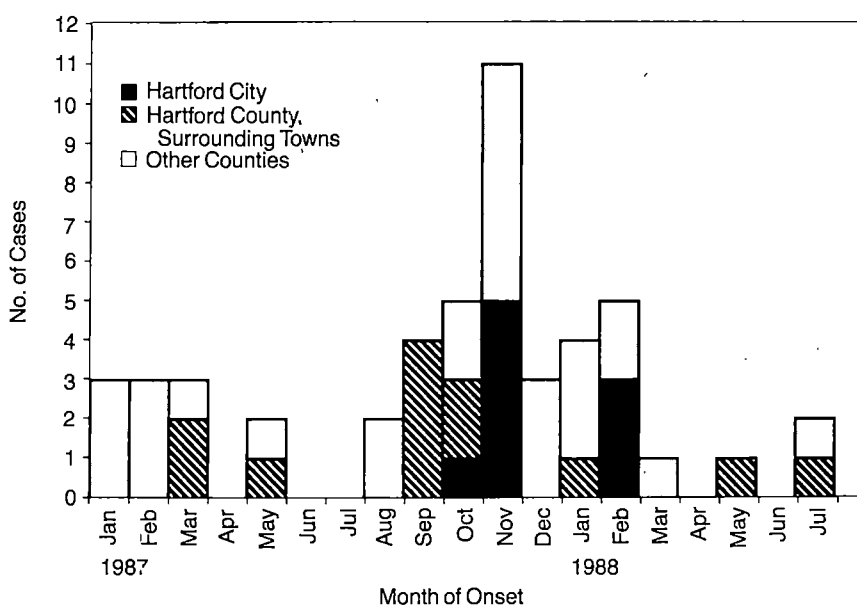
Case Series and Case-Control Study

We reviewed inpatient and outpatient records on 14 of the 16 case children in Hartford County and 10 cluster-related case children who lived within 30 miles of Hartford County. Parents of these children were also interviewed to determine the frequency, severity, and duration of symptoms.

The same 24 children in the case series were also included in the case-control study. For each of 23 case children, 2 control children matched to the case child by age (± 1 year) and by race/ethnicity were randomly selected from the active medical records of the case child's primary care provider. Only 1 control child could be matched with the remaining case child. Parents of case and control children were interviewed using a standard questionnaire that collected information on some 30 different items, including the following: antecedent symptoms, drugs, home remedies, foods, insect bites, travel, and school or day-care attendance in the month prior to the case child's HSP onset day. Information was also obtained on home environment, drinking water supply, illness in family members, and the child's medical history. The interviews took place a median of 38 days after the onset of HSP, with a range of 2 to 122 days.

At the time of the interview and after informed consent was obtained, blood samples were drawn from 21 of the 24 case children and 18 participating Hartford County control children. This blood was taken more than 2 weeks after HSP onset in 17 of the 21 case children and between 2 and 7 days after HSP onset in the other 4. The sera were stored and later tested using complement fixation and indirect fluorescent antibody techniques for antibodies to the following agents: adenovirus, coxsackievirus (serotypes A16 and B1 to B6), *Legionella pneumophila*, parainfluenza (serotypes 1 to 3), parvovirus B19, *Mycoplasma pneumoniae*, and group A *Streptococcus*. Evidence of recent streptococcal infection was defined as a reciprocal antistreptolysin O or anti-deoxyribonuclease B titer of 320 or greater in any serum specimen.

In our estimate of the risk of illness in Hartford County by race/ethnicity, we controlled for socioeconomic status (census tract median household income greater or less than \$10 000 per year) and area of residence (Hartford city vs surrounding towns) by creating stratified 2×2 tables and using Mantel-Haenszel estimators.¹³ In the case-control



Henoch-Schönlein purpura cases by month of onset in Connecticut from January 1987 through July 1988. Eight of the nine cases from Hartford city were in Hispanics.

study, odds ratios were calculated using both unmatched and matched-pair analysis. The results of these analyses were very similar; for simplicity, only the matched odds ratios are presented. Confidence intervals were calculated using methods of Robins et al.¹⁴ The potential of confounding as the cause of the association between acetaminophen and illness was evaluated with a conditional logistic regression model that included sore throat, fever, and acetaminophen use as independent variables. Because of the small number of children in the study, several case-control differences were found with substantial odds ratios, but the confidence interval overlapped 1.0. To avoid overlooking what may be clues to the etiology of HSP and to allow readers to judge whether these differences are important, we have reported these differences and provided both the odds ratios and confidence limits.

RESULTS

Descriptive Epidemiology

The identified cases of HSP are shown by month of onset in the Figure. Within Hartford County, 16 children became ill with HSP during the cluster time from August 1, 1987, to February 29, 1988 (incidence, 1.7/10 000 per year). This number of cases was more than five times the number of cases that occurred in the preceding 7 months (3 cases; incidence, 0.3/10 000 per year). The 16 cluster-related case children in-

cluded 10 (63%) boys and 6 (38%) girls; the median age was 5 years (range, 2 to 9 years). There were 7 white, 1 black, and 8 Hispanic children.

Hartford County contains the city of Hartford (population, 136 392), which has a primarily minority and lower-socioeconomic-group population, and Hartford's surrounding towns, which have a population that is overwhelmingly white and primarily of middle or upper-middle socioeconomic status. Eight of the nine Hartford city case children were Hispanic (all of Puerto Rican ancestry) and the other was black. These nine children themselves clustered in two distinct time periods within the larger cluster; six children became ill between October 15 and November 25, and three became ill between February 5 and February 21 (Figure). Included in this group were two pairs of siblings in Hispanic families.

Table 1 shows the incidence in Hartford County of cluster-related cases by area of residence, race, and census tract socioeconomic level. The incidence was particularly high in Hartford city (4.8/10 000), and within Hartford city the incidence was high among Hispanics (12/10 000) and children in lower-socioeconomic-group census tracts (7.0/10 000). Race, socioeconomic status, and area of residence were closely

Table 1.—HSP* Incidence in Hartford County, Conn., by Race, Socioeconomic Status, and Area of Residence Between August 1, 1987, and February 29, 1988

	Hartford City		Surrounding Towns		Entire County		Relative Risk (95% Confidence Interval)
	No. of Cases	Incidence†	No. of Cases	Incidence†	No. of Cases	Incidence†	
Race/ethnicity							
Hispanic	8	12.0	0	...	8	8.6	9.5 (3.4-26)
Black	1	1.3	0	...	1	0.9	1.0 (0.1-8.0)
White	0	...	7	1.0	7	0.9	1.0 (Reference)
Socioeconomic status (census tract median household income)							
<\$10 000/y	6	7.0	0	...	6	6.9	6.1 (2.0-18)
≥\$10 000/y	3	3.0	7	0.9	10	1.1	1.0 (Reference)
Total	9	4.8	7	0.7	16	1.7	...

*HSP indicates Henoch-Schönlein purpura.

†This is the number of cases per 10 000 children under 15 years of age per year.

correlated. However, when we attempted to control for socioeconomic status and area of residence, there was still a large relative risk for illness among Hispanics compared with blacks (relative risk, 8.6; 95% confidence interval [CI], 1.2 to 60) or whites (relative risk, 15.0; 95% CI, 0.6 to 36).

The time-clustering observed was not limited to Hartford County. In the seven other counties of Connecticut we identified 18 additional children in whom HSP occurred between August 1, 1987, and February 29, 1988, compared with only 8 children during the preceding 7 months (Figure). Sixteen of these children were white and 2 were Asian; none was Hispanic. During the entire time for which we collected reports, we identified no cases among Hispanic children (and only 2 cases in non-Hispanic children) in Bridgeport (population 142 546) and New Haven (population 126 109), which are demographically similar to Hartford and where our methods of finding cases were as intensive as in Hartford.

Case Series and Case-Control Study

For the 24 cluster-related case children included in the series, the most common clinical manifestations were rash (24 children, 100%) and joint pain and/or swelling (21 children, 88%), most commonly in the knees and ankles. Nineteen children (79%) complained of abdominal pain, but this pain lasted longer than 1 day in only 11 children

(46%). Nine children (38%) experienced vomiting. Of the 21 children with documented urinalyses, 4 (19%) had hematuria, defined as 10 red blood cells per high-power field. The median duration of rash was 14 days, with a range of 4 to 42 days; the median duration of joint symptoms was 5 days, with a range of 1 to 75 days. In addition to the two sibling pairs in the study, 1 child had a history of HSP in a first-degree relative.

Laboratory findings on these 24 children were consistent with the diagnosis of HSP. Eighteen (95%) of 19 children had platelet counts greater than $0.25 \times 10^{12}/L$. The erythrocyte sedimentation rate was greater than 35 mm/h in 5 (33%) of 15 children tested. Antinuclear antibodies and rheumatoid factor were not found in any of the 4 patients tested. The serum IgA level was elevated in 1 of 4 children and borderline in 1 other child. Eleven children had throat cultures sent at the time of diagnosis either because of a history of a sore throat or because of a concern that group A *Streptococcus* had a causal role in HSP. Six (55%) of these cultures were positive.

Eleven children (46%) were hospitalized for a median of 3 days, most often for diagnostic purposes or for abdominal pain or vomiting. Two children had barium enemas, which did not show intussusception. No other children had any major diagnostic or therapeutic procedures. At the time of the interview, one child had active nephritis; otherwise, none had had serious complications and

none had suffered sequelae.

The socioeconomic status and area of residence of the 24 case children and the 47 matched control children are presented in Table 2. The matching process had the effect of selecting controls who were very similar to cases in these demographic features.

The presence of antecedent symptoms and exposures to drugs in cases and controls is shown in Table 3. Case children were more likely than control children to have had a sore throat in the month prior to HSP onset (52% vs 22%; odds ratio [OR], 3.8; 95% CI, 1.1 to 13). This difference in the frequency of previous sore throat was seen in both Hispanics (43% vs 13%; OR, 2.4; 95% CI, 0.4 to 14) and non-Hispanics (56% vs 26%; OR, 5.5; 95% CI, 1.0 to 31) and was greater among children interviewed within 30 days of disease onset (6 [67%] of 9 cases vs 3 [21%] of 14 controls; OR, 9.6; 95% CI, 0.8 to 110).

Smaller differences between cases and controls were seen in the frequency of fever and nasal discharge (Table 3). Case children were no more likely than control children to have gastrointestinal complaints. Visits to physicians for illness during the 30 days prior to HSP onset were more common among cases than controls (30% vs 11%; OR, 3.3; 95% CI, 0.8 to 13). Six of the seven case children who made visits to physicians did so because of respiratory symptoms.

Acetaminophen was taken more often by case children than control children

Table 2.—Selected Demographic Features of HSP* Case and Control Children		
	No. (%) of Cases	No. (%) of Controls
Socioeconomic status (household income)		
<\$10 000/y	8 (33)	13 (28)
\$10 000-\$29 999/y	5 (21)	15 (32)
≥\$30 000/y	11 (46)	18 (38)
Unknown	0	1 (2)
Area of residence		
Hartford city	9 (38)	17 (36)
Hartford County, surrounding towns	5 (21)	10 (21)
Other counties	10 (42)	20 (43)

*HSP indicates Henoch-Schönlein purpura.

Table 3.—Symptoms and Exposures Within 30 Days Before HSP* Onset			
Symptom or Exposure	No. (%) of Cases	No. (%) of Controls	Matched Odds Ratio (95% Confidence Interval)
Sore throat	12/23 (52)	10/46 (22)	3.8 (1.1-13)
Fever	10/23 (43)	10/47 (21)	2.3 (0.8-6.3)
Nasal discharge	11/23 (48)	16/46 (35)	1.8 (0.7-4.8)
Cough	9/24 (38)	15/46 (33)	1.1 (0.4-3.0)
Vomiting/diarrhea	3/24 (13)	8/47 (17)	0.7 (0.2-3.0)
Acetaminophen	14/23 (61)	14/46 (30)	2.9 (1.1-7.9)
Aspirin	0/23 (0)	2/47 (4)	0 (0-11)
Antibiotic	4/24 (17)	9/47 (19)	0.8 (0.2-2.8)
Cough or cold medicine	9/24 (38)	16/46 (35)	1.0 (0.4-2.8)

*HSP indicates Henoch-Schönlein purpura.

during the month prior to HSP onset (61% vs 30%; OR, 2.9; Table 3). However, when we controlled for the presence of upper respiratory tract symptoms with a conditional logistic regression model, this difference was no longer present (OR, 1.6; 95% CI, 0.5 to 5.7). Cases and controls were approximately equally likely to have taken an antibiotic (17% vs 19%; OR, 0.8). Interestingly, of the 12 case children with sore throat, only 3 (25%) had taken an antibiotic, compared with 6 (60%) of the 10 control children with sore throat.

Three other differences between cases and controls were found that, due to small numbers, had marginal statistical power, but that were consistent with other findings suggestive of an infectious cause. Case children more frequently than control children had a household member with upper respiratory tract symptoms during the month before or the month after HSP onset (63% vs 38%; OR, 3.4; 95% CI, 1.0 to 12). Case children also tended to live in a more crowded environment, as indicat-

ed by households with more than one person per room, in spite of effective matching for socioeconomic status (38% vs 28%; OR, 2.0; 95% CI, 0.6 to 7.1). More case children than control children under the age of 5 years attended day care (7 [78%] of 9 cases vs 7 [47%] of 15 controls; OR, 3.3; 95% CI, 0.5 to 20). No other substantial differences between cases and controls were found for any of the other risk factors evaluated.

Because of the high incidence in Hispanic children, an effort was made to identify unusual ethnic foods or home remedies associated with illness. None was reported by parents of either cases or controls.

Antibody evidence of recent streptococcal infection (Table 4) was present slightly less often in cases than controls in Hartford city (56% vs 77%; OR, 0.7; 95% CI, 0.2 to 3.5) and in Hartford County as a whole (50% vs 67%; OR, 0.4; 95% CI, 0.1 to 2.3). However, evidence of recent streptococcal infection was present more often in both case and control children in the city of Hartford (15

Table 4.—Antibody Evidence of Recent Streptococcal Infection Among HSP* Case and Control Children		
Area of Residence	No. (%) of Cases	No. (%) of Controls
Hartford city	5/9 (56)	10/13 (77)
Hartford County, surrounding towns	2/5 (40)	2/5 (40)
Other counties	1/7 (14)	0

*HSP indicates Henoch-Schönlein purpura.

[68%] of 22) than in case and control children in other towns (5 [40%] of 17; OR, 5.1; 95% CI, 1.1 to 26).

At the time of the interview, no more than two case children statewide had elevated levels of antibodies to any of the other agents listed in the "Methods" section. Blood was also available from the time of HSP onset for six case children, providing paired samples to test for antibody changes. One acute-convalescent pair showed a fourfold titer rise in antibody to *L pneumophila*. None of these six pairs showed a fourfold increase or decrease in antibody to any of the other agents, including group A *Streptococcus*. To determine the ability to make immunoglobulins to specific challenges, we tested serum samples from case and control children for antibody to cytomegalovirus and rubella. Approximately 75% of both case and control children had antibodies to these two viruses.

COMMENT

Although children with HSP generally recover uneventfully, severe complications can occur. In approximately 8% of children, gastrointestinal hemorrhage or intussusception occurs.² Twenty to forty percent of children have clinically apparent glomerulonephritis,^{2,3} and in 3% to 14% of these children disease progresses to chronic renal insufficiency.^{2,4} Henoch-Schönlein purpura was the cause of renal failure in 2% and 5% of groups of children undergoing hemodialysis in California and France, respectively.^{15,16} The importance of understanding the epidemiology, etiology, and pathogenesis of HSP lies in the potential prevention of renal failure in these children.

The clinical manifestations of the children in our study were similar to those in children in previously published case series.^{2,3} Although the character of the illness was typical, the pattern of occurrence of the disease in the population was not.

Our intensive case finding in Hartford County for 1987 placed the background incidence of HSP among children under age 15 years at approximately 0.2 to 1.0 cases per 10 000 children per year. This is comparable with the incidence of HSP found by Nielsen¹⁷ in a study of the epidemiology of HSP in Denmark. Nielsen found conflicting results regarding the pattern of disease occurrence but wrote that "the conclusion is clear: there is no clustering." In contrast, we were able to demonstrate a case cluster limited in time and space and centered in one ethnic group. While a seasonality of occurrence of the HSP has been described previously, with the winter months the peak time period,^{3,18} to our knowledge, this is the first published report of such a cluster.

Extremely high incidence rates were present in a single demographic group: lower-socioeconomic-group Hispanic children from the city of Hartford. When we attempted to control for urban environment and socioeconomic status, the incidence rate for Hispanics was still far higher than for white or black non-Hispanic children. It is possible that cases of HSP were missed in black children because the rash might be less prominent; however, a reporting artifact such as this could not explain the low observed rate in white non-Hispanic children. Thus, it appears that while socioeconomic or urban factors such as crowding may have contributed to the development of illness, some other factors associated with Hispanic children in this outbreak caused them to be at uniquely high risk for HSP.

Since the Hispanic children in our study were all of Puerto Rican ancestry, a possible explanation for their high incidence rates is that members of this ethnic group have a higher immunologic susceptibility to HSP than other Americans. This might explain the finding of two sibling pairs in Hispanic families with HSP. Other authors have noted HSP occurrence in two or more family

members.^{3,20} Alternatively, the sibling pairs and the other Hispanic children in the study may have been exposed to a common factor—such as an ethnic food or home remedy—that increases the likelihood of illness. While we carefully sought information about this kind of common exposure and found none, we are not certain that an exposure specific to this ethnic group did not take place.

Histologically, HSP is characterized by leukocytoclastic vasculitis,²¹ which is apparently caused by IgA immune complexes.^{6,22,26} Henoch-Schönlein purpura may occur when certain specific agents provoke an immune response in a predisposed host that leads to the formation of these IgA immune complexes.

The association between HSP and previous upper respiratory tract symptoms suggests that common exposure to an infectious agent that caused respiratory symptoms provided the immunologic stimulus for the development of HSP in the cluster-related case children. While previous case series have reported a high frequency of antecedent upper respiratory tract infection in children with HSP,^{2,3,18,19} we believe our study is the first to compare this frequency with that of a matched control group. It seems unlikely that the association with a previous upper respiratory tract infection can be explained by recall bias in view of the findings of the larger case-control differences among those families interviewed most recently and the association with previous physician visits, which are more objective indicators of illness.

If an upper respiratory tract infection was the inciting event in the development of HSP, it is not surprising that we also found a greater number of upper respiratory tract infections in other members of case households. The observed differences between case and control children in household crowding and day-care attendance (in spite of close socioeconomic matching) are also consistent with the hypothesis that the agent causing these upper respiratory tract infections is transmissible person-to-person in crowded settings.

Many infectious agents have been proposed as causes of HSP. It was previously thought that cases could often be linked to recent infection with group A *Streptococcus*.²⁷ Our investigation

produced three findings that provided some support for a relationship between group A *Streptococcus* and HSP in this cluster: (1) The organism was found on throat cultures of 6 of 11 case children. (2) Case children with sore throats received antibiotics less often than controls, suggesting a protective effect of antibiotics. (3) Serologic evidence of recent streptococcal infection was more frequent in Hartford city—the area with the highest incidence of HSP—than in the rest of Hartford County or in other areas of the state. However, these findings need to be interpreted cautiously because of the small numbers of children in this study. Furthermore, we were unable to show a greater frequency of elevated streptococcal antibody titers in cases than controls. This lack of association between streptococcal antibodies and HSP has also been found in a previous case-control study.²⁸ We believe, therefore, that although the data do not support a simple and direct causal role for group A *Streptococcus*, it remains possible that recent streptococcal infection was one contributing factor in the development of HSP in case children.

The absence in nearly all case children of antibodies to the other agents for which testing was performed suggests that they were unimportant in this cluster. In particular, we found nothing to support the role of parvovirus B19, which has recently been proposed as a cause of HSP.¹²

Overall, the findings of our case-control study are consistent with the conclusion that HSP can result from a reaction in a susceptible host to a communicable infectious agent. We believe that during periods of high prevalence of such an infectious agent, the interactions between host, agent, and environment could account for the type of case clustering we found. Similar investigations of HSP clusters are needed to better characterize risk factors for HSP and to identify agent(s) that have a causal role in this disease.

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Breast-feeding Pattern Among Indochinese Immigrants in Northern California

Eunice Romero-Gwynn, PhD

• A sharp decline in the rate of breast-feeding was documented among Indochinese mothers who migrated from Cambodia and Laos to a city in northern California. While 97.0% of the mothers breast-fed their last infant born in Indochina, only 26.1% and 22.4%, respectively, breast-fed their first and last infant born in the United States. Furthermore, only 3.8% of the mothers who were pregnant at the time of the study intended to breast-feed. The duration of breast-feeding decreased from an average of 20.4 months for the last infant born in Indochina to 8.7 months for the last infant born in the United States. After controlling for several sociodemographic variables, only formula samples distributed at hospital discharge had a significant association with formula feeding (odds ratio, 2.02). However, data on intention to breast-feed suggested that a clear cause-and-effect relationship may not exist. Factors related to cultural traditions and acculturation are offered as possible explanations for the decline in breast-feeding. Breast-feeding education for mothers and training for health professionals is recommended.

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Internal and international migration have been associated with improvement in family well-being and the diets of adults.^{1,3} However, changes in infant feeding among families who have emigrated from less industrialized to more industrialized settings have been less positive.⁴⁻¹⁰ The common pattern seen in most studies is a rapid decline in breast-feeding, coupled with an increase in use of commercial formula and other manufactured supplementary foods for infants after emigration. A decline in the rate of breast-feeding was documented by Evans et al,⁴ who studied mothers

who emigrated from northern India to England, and by Goel et al⁵ among Pakistani, Indian, Chinese, and African mothers who emigrated to Scotland. Among the groups who emigrated to the United Kingdom, the Chinese appeared to have experienced the greatest decline (from 98.0% to 2.0%) in breast-feeding before and after emigration. Other researchers have documented declines in breast-feeding among Asian mothers who emigrated to Sweden⁷ and to Australia,⁸ and among Mexican mothers who moved to the United States.^{9,10} A different trend was reported from two studies conducted in the mid-1980s among Turkish women who emigrated to Stockholm, Sweden,⁷ and Vietnamese mothers who emigrated to Australia.¹⁰ In both of these studies, mothers who emigrated had breast-feeding rates similar to the prevalent rate in the host society.

The present study was motivated by reports from nutrition education assistants working for the Expanded Food and Nutrition Education Program, who observed frequent use of formula among Indochinese families, and by our own observations in several homes. This study was planned to quantify the observations and to test the hypothesis that the incidence of breast-feeding among the refugee community had significantly declined as a result of emigration. Thus, the major purposes of the study were (1) to assess the incidence and duration of breast-feeding and weaning practices before and after emigration to the United States, and (2) to identify factors associated with both milk-feeding practice and weaning. The present report will focus on breast-feeding patterns before and after emigration. Weaning practices will be reported later in an article in preparation at this writing.

SUBJECTS AND METHODS

The sample consisted of 134 Indochinese refugee mothers who settled in a city in northern California. At the time of the study the refugee families were living in three large apartment complexes in one area of the city. Approval to conduct the study was obtained from the Human Subjects Committee of the University of California, Davis, and from local refugee community leaders.

The criteria for selection of mothers to participate in the study were that they must have at least one infant born in Indochina and at least one infant born in the United States. Mothers were selected after the completion of a door-to-door census in which the number of children born before and after emigration was ascertained. Mothers who met the criteria were then visited in their homes and invited to participate voluntarily in the study. Only 2 of the 136 selected mothers declined to participate. Since the intent of the study was to assess the pattern of infant feeding over time, mothers who had more than one infant born in the United States were asked about feeding practices for the first and last children born in the United States. Mothers who were pregnant at the time of the study (26 women) were asked if they had decided how they would feed their infant, and if so, what milk (breast, formula, both, other) they were planning to feed their infant after birth.

Data on infant feeding were collected using a questionnaire tested on Indochinese families who were from the same community but who did not meet the inclusion criteria. In the construction of the questionnaire, four members of the community were consulted regarding cultural appropriateness of the questions included. Individual interviews were conducted with each mother at home and in her native language (Hmong, Laotian, or Cambodian).

Statistical analysis consisted of frequency distributions, χ^2 analysis, and logistic regression.¹¹ Logistic regression is a nonlinear model that is used to explain binary dependent variables such as breast-feeding vs non-breast-feeding. The independent variables used in the regression analysis were as follows: parents' education, attendance to En-

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English classes, family type (nuclear vs extended), years of residency in the United States, participation in the Supplemental Food Assistance Program for Women, Infants and Children (WIC) during pregnancy, and the receiving of formula samples at hospital discharge. Odds ratios (which indicate the likelihood of the occurrence of a given phenomenon: breast-feeding vs non-breast-feeding) were calculated using the coefficient obtained in the logistic regression analysis.¹² The Statistical Package for the Social Sciences¹³ and the BMDP¹¹ packages were used for computer analysis.

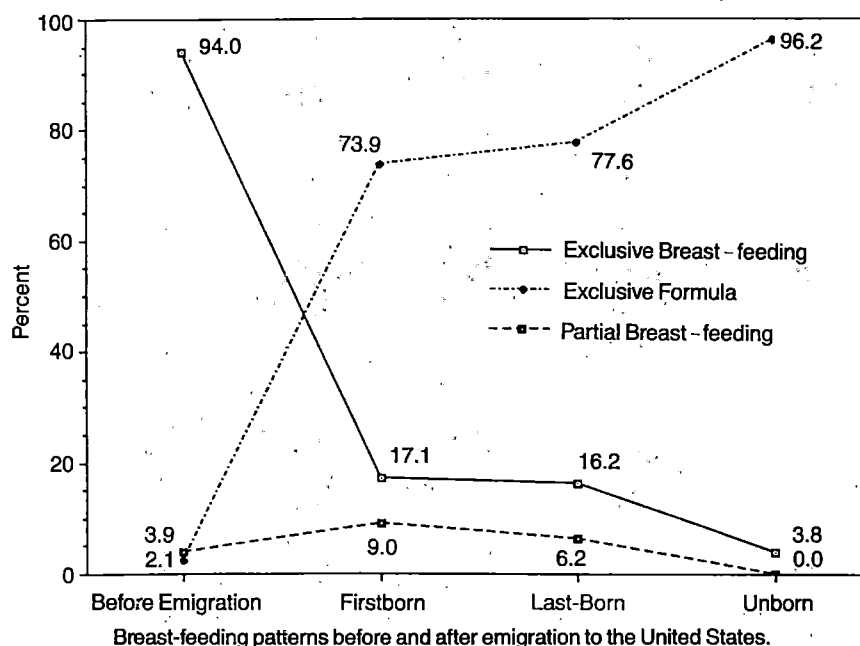
RESULTS

Description of the Sample

The sample consisted of 134 mothers and 348 children (134 last-born in Indochina before emigration, 134 first-born in the United States, and 80 last-born in the United States; 54 families had only one child born in the United States). The native languages of the mothers were Hmong (50.7%), Cambodian (32.1%), and Laotian (17.2%). Almost one half of the sample migrated with the parents of either the husband or wife or both. The majority of the mothers did not attend school in their country of origin; 24.4% had completed from 1 to 12 years of school. The majority of mothers (68.0%) had attended English classes in the United States for periods that varied from 1 to 36 months. Two percent of the mothers had enrolled in adult education classes or received other formal education in addition to English classes. Although the level of education of the husbands was higher than that of the wives, approximately one third of the husbands had received no formal education. More husbands than wives had attended school in the United States in addition to taking English classes offered for immigrants through local schools. The fertility rate among these families was high. The numbers of children born to them ranged from 2 to 12 (mean, 5.4 ± 2.2). The mean ages of the first and last children born in the United States were 2.4 years and 9.5 months, respectively.

Welfare was the main economic support for most families. Both husbands and wives practiced gardening in small lots around their apartment buildings and/or community gardens using land provided by local organizations. Medicinal herbs were invariably part of the garden, along with vegetables. Al-

	Infant Birthplace, %			
	Indochina (n = 134)	Firstborn (n = 134)	Last-Born (n = 80)	Unborn (n = 26)
Breast-fed				
Exclusive	94.0	17.1	16.2	3.8
Partial	3.9	9.0	6.2	0.0
Subtotal	97.9	26.1	22.4	3.8
Exclusive formula	2.1	73.9	77.6	96.2



though gardening mainly produced food for family consumption, some families were able to sell their produce in local markets. Families had access to food assistance programs such as the WIC and food stamps. Employment for either husband or wife was very rare; only 2.3% of the mothers had worked away from their homes.

Socialization among subgroups of immigrants sharing cultural traditions and languages (Hmong, Laotian, Cambodian) appeared to be very high. Groups of adults were often seen visiting inside their homes or in front of their apartments. Socializing with other ethnic groups seemed to be rare. However, a major means of contact with American culture was through mass media. Television sets and radios were observed in nearly every home; stereos and video-

cassette recorders were seen frequently.

Breast-feeding Before and After Emigration

Table 1 and the Figure show the incidence of exclusive breast-feeding, partial breast-feeding, and exclusive formula feeding for the last infant born in Indochina and for first and last infants born in the United States. They also show the breast-feeding intentions of those mothers who were pregnant at the time of the study. As can be seen in Table 1, 97.9% of the last infants born before emigration were breast-fed (94.0% exclusive breast-feeding and 3.9% partial breast-feeding), and 2.1% were fed milk other than breast milk. After emigration to the United States there was a sharp decline in breast-feed-

ing. Only about one sixth of the mothers breast-fed their first and last infant born in the United States. The trend continued toward an even greater decline since only 3.8% of the 26 women who were pregnant at the time of the study intended to breast-feed. Conversely, the number of mothers who fed their infants formula increased from 2.1% in Indochina to 73.9%, 77.6%, and 96.2% for the first, last, and expected infants in California, respectively. The duration of breast-feeding (in ever-breast-fed infants) decreased from an average of 20.4 months before migration to 8.7 months for the last infant born in the United States. A comparison of reasons for breast-feeding and for formula feeding is shown in Table 2. The two major reasons given by mothers for breast-feeding in their country of origin were related to the high cost or lack of availability of formula in their localities. Reasons given by mothers for formula feeding in the United States were (in order of frequency) intention to work, desire to attend school, lack of or insufficient milk, and breast infection. Other reasons given by smaller numbers of mothers are listed in Table 2.

Type and Source of Formula Used

Most mothers reported receiving formula samples at hospital discharge; 88.1% and 87.5% reported they had received samples for their first and last infant born in the United States, respectively. The types of formula given were (in order of frequency) Similac, Enfamil, SMA, Isomil, and Prosobee. Formula was obtained using WIC vouchers for 76.7% and 69.2% of the first- and last-born infants in the United States, respectively. Mothers who received formula from the WIC used it for different periods: 24.7% of them used it for 1 to 6 months, and 75.3% used it for 7 to 12 months. Families not participating in the WIC purchased formula for the entire feeding time. (The cost of feeding formula per infant per month is approximately \$70, or nearly \$850 per year, calculated in 1988 and based on the price of ready-to-feed formula that is commonly used by these families.)

Mothers were asked which, in their opinion, was the best milk for an infant. Their responses were "formula" (58.3%), "breast" (35.8%), "either one is

Reason	Infant Birthplace, No. (%)		
	Indochina	United States	
		Firstborn	Last-Born
Breast-feeding			
Formula very expensive	97 (77.6)	19 (82.7)	10 (76.9)
Formula not available	27 (21.6)
Doctor/nurse advice	1 (0.8)	1 (4.3)	...
Breast-fed previously	...	1 (4.3)	1 (7.7)
Better for infant's health	...	2 (8.7)	2 (15.4)
Subtotal	125 (100)	23 (100)	13 (100)
Formula feeding			
Intend to work	4 (50.0)	30 (27.0)	28 (41.8)
Intend to go to school	1 (12.5)	30 (27.0)	14 (20.9)
Lack of or insufficient milk	...	32 (28.9)	21 (31.3)
Breast infection	3 (37.5)	5 (4.5)	2 (3.0)
Mother prefers formula	...	3 (2.7)	1 (1.5)
Friend's influence	...	5 (4.5)	1 (1.5)
Doctor's advice	...	3 (2.7)	...
Cesarean delivery	...	3 (2.7)	...
Subtotal	8 (100)	111 (100)*	67 (100)†

*Includes exclusive formula feeding (n = 99) plus formula supplemented with breast milk (n = 12).

†Includes exclusive formula feeding (n = 62) plus formula supplemented with breast milk (n = 5).

good" (5.0%), and "don't know" (0.9%). Table 2 shows reasons given by mothers for breast-feeding and for formula feeding their infants. It is important to note that the first reason given by most mothers for feeding breast milk was the high cost of formula; only 2 (15.4%) of the 13 mothers who planned to breast-feed their expected infant mentioned breast milk as being "better for baby's health."

The type of family (extended vs nuclear) and the type of formula given at hospital discharge were the only two variables significantly related to feeding mode. Mothers living in extended-family households (with parents of either spouse) were more likely to breast-feed than those living in nuclear-family households ($\chi^2 = 8.91$; $P = .002$). Thus, 65.6% of the mothers living with their parents breast-fed their infants, as opposed to 34.4% who breast-fed while living on their own. However, not all couples living with parents breast-fed; 35.6% of the couples who formula fed had their parents living with them.

Mothers who received formula samples at hospital discharge were less likely to breast-feed ($\chi^2 = 40.14$; $P = .001$); 98.0% of the mothers who formula fed at

home received formula at hospital discharge. While these statistics suggest an association, a cause-and-effect relationship cannot be inferred. None of the other characteristics of the family, such as education of the couple, years in the United States, number of children, attendance to English classes, ethnic subgroup (Hmong, Cambodian, Laotian), or participation in the WIC program, were related to the infant-feeding mode.

Results of the logistic regression analysis showed that mothers who received formula samples at hospital discharge were more likely to feed their infants formula than were mothers who did not receive such samples (odds ratio, 2.02; $P = .05$). The type of family (nuclear vs extended), which was a significant factor in the χ^2 analysis, was not significant in the regression analysis. None of the other independent variables studied showed any significant role in explaining feeding mode.

COMMENT

In the present study group, a sharp decline in breast-feeding began with the first infant born in the United States and continued with subsequent births.

Thus, while 97.7% of mothers breast-fed (94.0% breast-fed exclusively) their last infant born in Indochina, only 26.1% and 22.4%, respectively, breast-fed their first and last infants born in the United States. Furthermore, only 3.8% of the mothers who were pregnant at the time of the study were planning to breast-feed.

Our statistics demonstrating a decline in the rate of breast-feeding after emigration are similar to those reported by Evans et al⁴ and Goel et al⁶ among Indian and Chinese mothers who emigrated to the United Kingdom. For example, the incidence found by Evans et al⁴ among Indian mothers was 92.0% before emigration and 30.0% after emigration. The duration of breast-feeding among these mothers decreased from 10.2 months in India to 1.1 months in the United Kingdom. In our sample, the average duration of breast-feeding was 20.4 months for the last infant born in Indochina, as opposed to 8.7 months for the 18 mothers who breast-fed their last infant born in California. Our figures for breast-feeding incidence are lower than those reported from Mexican mothers who have emigrated to California⁹ and Indochinese mothers (mostly from Vietnam) who have emigrated to Australia.^{8,10} Mathews and Manderson⁸ reported a breast-feeding incidence of 75.0% and 40.0% (for ever-breast-fed infants) before emigration from Indochina and after settlement in Sydney, Australia, respectively. The study by Reynolds et al¹⁰ in Perth, Australia, seems to be the first published research documenting no decrease in breast-feeding after emigration. The authors even suggest the possibility that an increase may have taken place. Their figure for breast-feeding initiation among these Vietnamese mothers was 81.0%. The large difference in breast-feeding initiation between our sample and that studied by Mathews and Manderson⁸ and Reynolds et al¹⁰ may be due to differences in the samples. The mothers in those two studies were primarily Vietnamese, while the mothers in the present study were all Laotian or Cambodian. Although the level of education was not reported by Mathews and Manderson⁸ or Reynolds et al,¹⁰ it is known that, in general, the persons who emigrated from Vietnam in the 1970s

tended to be educated, wealthy, and greatly influenced by European culture. The refugee mothers in our sample were mainly from villages and remote areas of Laos and Cambodia. Approximately two thirds of them had not received formal education.

Reynolds et al¹⁰ indicated that the Vietnamese women studied in Perth assimilated the infant-feeding practices of the host communities, as the incidence and duration of breast-feeding in their sample was very close to that of the native Australian mothers in Perth (81.0% vs 82.0%). Thus, it is possible that the Vietnamese immigrants were integrated into the Perth community and had the opportunity to perceive accurately the local infant-feeding practices prevalent there. The integration of families in our sample with a cross-section of the large community in Stockton seemed to be very limited. This may be due to limited English skills, lack or limited means of transportation from housing, or lack of or limited participation in the labor force.

While in many other countries breast-feeding is commonly practiced in public, in the United States breast-feeding is seen neither in public nor in the mass media. Bottle-feeding, however, is very often seen in public places in the United States, creating an inaccurate representation, and possibly projecting the notion that breast-feeding is not practiced in the United States.

Although there are no data on breast-feeding among the general population of mothers in Stockton, the 1984 data obtained by Martinez and Krieger¹⁴ on low-income mothers (<\$7000 per year) indicate a breast-feeding incidence of 36.6% vs 71.8% for mothers in the above-\$25 000 income bracket. If the national figures for the lowest income group are close to the incidence of breast-feeding among low-income families in Stockton, the assimilation explanation given by Reynolds et al¹⁰ may apply to our sample of mothers. Their rates for ever having breast-fed were 26.1% and 22.4%, respectively, for the first and last infants born in the United States. The assimilation concept may explain the difference between the breast-feeding rates among our sample of Indochinese persons and the Mexican immigrant mothers studied by Kokinos and Dewey.⁹ The

breast-feeding incidence among the Mexican mothers in first infants born in the United States was 58.0%, vs 26.1% for the first infants born in the United States in our Indochinese sample. However, the emigration characteristics are different among these two groups of mothers. As reported by Kokinos and Dewey,⁹ many of the Mexican mothers return to Mexico annually. This and the large Mexican culture existing in California may be delaying the assimilation of infant-feeding practices prevailing among other groups with limited income and education in the United States. In contrast, the emigration of our Indochinese subjects was more permanent because of their refugee status, which automatically granted them permanent residence in the United States. The distance between the United States and Indochina and the political situation in Indochina also severely limit contact with their original culture.

Another possible explanation for the decline in the popularity of breast-feeding could be the availability of infant formula in commercial outlets, hospitals, and supplementary food programs. Evans et al,⁴ explaining the decline in the rate of breast-feeding among Indian mothers who emigrated to England, claimed that the availability of an alternative to human milk and the means to obtain it may be the major cause for emigrant mothers to cease breast-feeding. When mothers in our sample were asked why they breast-fed their infants in Indochina, the two main reasons given were that formula was too expensive and/or it was not available (Table 2). No mention was made of a tradition of breast-feeding, nor was mention made of any nutritional or health-related attribute of human milk over other milk. This seems to suggest that the mothers in our sample did not know of the substantial advantages of human milk over commercial formula and that they would have fed formula to their infants in their native countries had it been available at an affordable price.

According to mothers' reports, in the United States formula samples were given at hospital discharge to 81.1% and 87.5%, respectively, of the mothers for their first and last infants born in the United States. This was the only variable showing statistical significance in

the logistic regression analysis when sociodemographic variables were controlled for. However, a clear cause-and-effect relationship cannot be deduced, as it is not known to what extent formula samples were accepted because mothers had already decided not to breast-feed their infants. In our study, prepartum breast-feeding intentions were not assessed for the first and last children born in the United States. However, 96.2% of the mothers (n=26) who were pregnant at the time of the study expressed their intention to feed formula exclusively to their expected infant.

A final possible explanation may be related to Indochinese cultural beliefs and practices surrounding delivery and puerperium.^{8,15} According to Indochinese beliefs, puerperium is a time of vulnerability for the mother, who is believed to lose "vital energy and heat" and to enter into a "cold state."¹⁵ This is counteracted by keeping her warm and confined for at least 1 month in a room that is sealed against wind and drafts. The woman is fed chicken and other foods considered "hot."^{8,15} She receives steam baths and is kept very warm with the heat of burning charcoal, a practice known as "mother roasting."^{8,15} Colostrum is not fed to the infant, as it is considered unhealthy. Thus, colostrum is usually expressed and discarded. The newborn is fed by another nursing mother or is fed rice water for the first 2 or 3 days. Breast-feeding is initiated when the production of colostrum ceases.⁸

A traditional practice in support of breast-feeding is that the mother's mother takes over the household work and cares for the family so the new mother can rest and care for her new infant.

It is not known to what extent an Indochinese mother's negative attitude toward feeding colostrum to the infant may be interpreted by the American hospital staff as a refusal to breast-feed, resulting in formula feeding during the hospital stay. Formula feeding in turn may be interpreted by the mother as the accepted infant-feeding practice in the United States. However, while this may have been the case for the first delivery in the United States, our data on intentions to breast-feed among women who were pregnant at the time of the study suggest that most mothers enter the hospital having made the decision to formula feed already.

Our study of a group of Indochinese immigrant mothers of childbearing age has demonstrated that their rate of breast-feeding has declined sharply following emigration to the United States. While the statistical analysis identifies formula samples given at hospital discharge as the major factor associated with the change, alternative explanations include the assimilation of the low breast-feeding rate typical of families with limited income and education in the United States, a distorted perception of formula feeding as the American infant-feeding norm, a disruption of traditional rituals surrounding partum and puerpe-

rium by delivery in the hospital vs traditional home delivery in Indochina, and, above all, lack or limited awareness of the advantages of breast-feeding for the health of the infant and the mother. The retrospective nature of the present study, which was based on mothers' recall of events, should be taken into account when interpreting our results. Prospective follow-up studies are recommended. Education on the importance of human milk, including colostrum, seems to be necessary for Indochinese mothers. Use of audiovisual aids showing American women breast-feeding may be helpful in changing these mothers' apparently mistaken perception of recommended infant feeding practices in the United States. Training for hospital staff regarding cultural factors and ways to assist mothers in initiating breast-feeding in the hospital, limitation of infant formula supplementation in the hospital, and limitation of the distribution of formula samples at hospital discharge are recommended.

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Educational Interventions

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Purpose.—This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.

Editorial Comment.—*Many training programs offer continuity clinic experiences for resident education. Some residents may grumble that this experience does not reflect the "real world." In this study, Wilson et al address this question and find, at least in their setting, that such an experience does indeed reflect the primary care experiences met by private pediatric practices in their community.*—H.D.A.

Does a Residents' Continuity Clinic Provide Primary Care?

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• Pediatric residents are required to care for a group of children over a period of time. For many, this "continuity" experience is in a hospital outpatient department that may or may not provide primary care. We applied a measure of primary care to the Primary Care Clinic, the continuity clinic at The Johns Hopkins Hospital, Baltimore, Md, and found that it compared favorably with private pediatric practices in the Baltimore area, providing significantly more "principal care" (93% vs 84.5% of encounters), and to the Harriet Lane Home walk-in clinic, where only 51% of encounters were "principal care." The Primary Care Clinic scored higher on a primary care index, a measure of the extent to which the facility serves as a primary care source for patients, suggesting that hospital-based training can provide residents with an opportunity to provide primary care.

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To balance the subspecialization of the past 2 decades¹ and to meet the requirements of the Accreditation Council for Graduate Medical Education for continuous care of patients,² pediatric resident training in many hospital-based outpatient clinics has been restructured to include provision of ongoing care for children, both for health maintenance and acute problems. These "continuity clinics" are organized within the hospital or the pediatrics department of the medical school to provide experience that will mimic as closely as possible pediatric practice as it takes place in the community.

One characteristic of ambulatory pediatric practice is the provision of primary care.^{3,5} Therefore, one measure of the appropriateness of a hospital-based clinic as an ambulatory or continuity training site may be the degree to which it provides primary care. We are aware of few previous reports of the measurement of primary care or its attributes in teaching clinics.^{6,7}

Although definitions vary, it is generally accepted that the concept of primary care refers to care that is accessible (including being open to new nonreferred patients), comprehensive (including both health maintenance and care for common acute illnesses), coordinated, and longitudinal.^{8,9} While there

appears to be consensus on what is meant by primary care, there is as yet little agreement on how to measure it.⁹ A list of indicators has been offered that, if present, suggest the potential for providing primary care.¹⁰ Physicians have made judgments about whether or not they provide the "majority" of care for a series of patients.¹¹

Measurement of the process of care has also been attempted. Attributes of primary care, for instance, continuity (longitudinality) and coordination, have been measured.^{6,7,12}

Weiner and Starfield¹³ developed an index of primary care that focuses on the process of practice and can be applied to a series of patient encounters with a practitioner, an office, or a clinic of any specialty. The index has been used previously to measure the degree to which a large number of office-based private practitioners in the Baltimore, Md, area, including pediatricians, are providing primary care. Based on observations made at patient encounters, among the advantages of the index are that it includes several aspects of primary care: accessibility, comprehensiveness, and longitudinality.

We used the index to measure the level of primary care in the Harriet Lane Pediatric Primary Care Clinic (PCC), the pediatrics house officers' continuity

clinic at The Johns Hopkins Hospital. The PCC is located in a tertiary care teaching center with a large pediatric house staff and a subspecialty and research orientation. Forty percent of the patients, who are predominantly from poor urban families, have at least one chronic problem. For these reasons and others, it was feared that the PCC might fail to provide the high level of primary care that was intended. This evaluation was designed to provide a basis for change if such was required.

PATIENTS AND METHODS

Data for calculation of an index of primary care, as previously reported, are obtained from patient encounter logs and based on the answers to questions addressed to consecutively seen patients or their parents.¹³ With wording modified for use in an exclusively pediatric clinic study, the questions were as follows:

1. Is this the child's first visit to this clinic?
2. Did a doctor from some place outside of this hospital send you to this clinic?
3. The last time this child had a regular checkup, did he or she go somewhere else or come here? Was it within the past year?
4. The last time this child received medical care for a bad cold or flu, did he or she go somewhere else or come here? Was it within the past year?

Answers are used to categorize each patient encounter into one of four broad categories of care: principal (PC) care, first-encounter (FE) care, specialized (SP) care, and consultative (CN) care. Defined in Table 1, the categories are listed in order beginning with the one thought most indicative of primary care. They are, therefore, listed in decreasing order of contribution to the index. Simply stated, a PC care encounter is a part of longitudinal care that includes both preventive services (question 3 above) and care for common acute illnesses (question 4 above) and adds the greatest weight to the index. Consultative care is a referral for a particular problem; because it is least indicative of primary care, it adds nothing to the numerator of the index. The classification algorithm is summarized in Table 2.

The four questions were asked by one of the two clinic registrars and answered by the adult accompanying each of 422 patients consecutively presenting for care to the PCC in the autumn of 1981. The responses were recorded on a log along with a number of demographic variables routinely collected at the time of registration.

Each encounter was categorized according to type. The visits of each type were summed and weighted according to the following formula to develop the primary care index¹³:

Category	Definition
Principal care (PC)	The patient receives ongoing nonreferral care for both preventive and acute day-to-day problems
First-encounter care (FE)	The patient is visiting the practice for the first time, but not by referral from an outside physician
Specialized care (SP)	The patient is receiving ongoing, nonreferral care for a particular problem or set of problems only
Consultative care (CN)	The patient is receiving care for a particular problem on referral by another physician

*Ordering of categories is from "most" to "least" indicative of primary care. From Weiner and Starfield.¹³

Care Category	Answers to Questions on Encounter Log			
	Referral	First Contact With Clinic	Last Checkup Here	Last Cold/Flu Care Here
Principal care (PC)	No	No	Yes or no†	Yes or no†
First-encounter care (FE)	No	Yes	No	No
Specialized care (SP)	No	No	No	No
Consultative care (CN)	Yes	Yes or no	Yes or no	Yes or no

*From Weiner and Starfield.¹³

†For an encounter to be classified as principal care, one of these two answers must be "yes."

$$\text{Index} = [(PC \times 1) + (FE \times 0.67) + (SP \times 0.33) + (CN \times 0)] / \text{Total No. of Encounters}$$

The index for the PCC was then compared with the analogous index for 20 Baltimore area private pediatric practices surveyed in late 1979.¹³ In addition, the percentages of encounters in each component of the index¹⁴ (ie, each care category) were compared, as were the percentages of patients reporting a checkup or cold/flu care within the previous year. The significance of observed differences was tested by χ^2 analyses of two-by-four and two-by-two tables.

The index was also calculated for the Harriet Lane Home (HLH), another Johns Hopkins hospital-based general pediatrics clinic. The HLH was staffed by faculty from the same division as the PCC and by pediatric house officers on block rotation, but was organized to be a "walk-in" clinic open for problem visits by patients with and without a regular source of care in the hospital or the community rather than to provide continuous primary care services. It had been observed that many parents who used community sources of medical care for "well-baby" visits brought their children to the HLH when the child was ill or had a particular type of problem. It was our hypothesis that the HLH was not providing a high level of primary care (that is, care that is not only accessible but comprehensive and longitudinal), and we believed that a measure useful in assessing pediatric practices should demonstrate that.

The questions previously used to classify

PCC encounters were addressed to adults consecutively bringing 211 patients for care at the HLH during specified half-days in the autumn of 1984 by a pediatric resident sitting at the registrar's desk. To provide a timely comparison, the index was once again calculated for the PCC using 162 consecutive patient encounters during exactly the same periods.

The χ^2 analyses of two-by-four tables were used to test the significance of differences noted between the HLH and the PCC and to assess the temporal stability of the encounter types in the PCC.

RESULTS

Of 422 adults questioned consecutively about the children they were bringing for care to the PCC in 1981, 20 could not or would not provide the answers to the questions. Of the remaining 402 encounters, 374 were indicative of PC care, 14 of FE care, 6 of SP care, and 8 of CN care.

In 1984, of 211 adults questioned about the children they were bringing for care to the HLH, 6 could not provide the necessary information. The classification of the remaining 205 was as follows: 105 were PC care, 48 were FE care, 43 were SP care, and 9 were CN care.

Of 162 adults questioned in 1984 about the child they were bringing to the PCC, 160 provided information. The en-

Table 3.—Number and Percent of Encounters in Categories of Care by Site and Time

	Time Period 1		Time Period 2	
	Baltimore Private Practices ¹⁴	Continuity Clinic (PCC)	Continuity Clinic (PCC)	Walk-In Clinic (HLH)
Year	1979	1981	1984	1984
No. of encounters	1254	402	160	205
Care category, No. (%)				
Principal care (PC)	1060 (84.5)	374 (93.0)	144 (90.0)	105 (51.0)
First-encounter care (FE)	94 (7.5)	14 (3.5)	8 (5.0)	48 (13.4)
Specialized care (SP)	37 (3.0)	6 (1.5)	0	43 (21.0)
Consultative care (CN)	63 (5.0)	8 (2.0)	8 (5.0)	9 (4.4)
Statistical values	$\chi^2 = 18.2$; $P < .001$	$\chi^2 = 6.6$; $P > .05$	$\chi^2 = 75$; $P < .001$	

Table 4.—Primary Care Index by Time and Practice Site

Site	Year	Primary Care Index
Private pediatric practitioners, mean	1979	79.9
Primary care clinic (PCC)	1981	95.8
Primary care clinic (PCC)	1984	93.4
Harriet Lane Home (HLH)	1984	73.9

Table 5.—Percent of Reported Care 'Here' in Past Year by Site

	Site and Year	
	Baltimore Private Practices (1979, N=1254) ¹⁴	Primary Care Clinic (1981, N=402)
Had checkup "here" in the past year, %	71.2	76.6 ($\chi^2 = 4.2$; $P < .05$)
Had cold/flu care "here" in the past year, %	60.2	68.7 ($\chi^2 = 9.4$; $P < .005$)

counters were classified as follows: PC care, 144; FE care, 8; SP care, 0; and CN care, 8.

The percentage of encounters fitting into each type of care for each of the sites and time periods is displayed in Table 3.

The PCC provided more PC care in 1981 than the sampled Baltimore area pediatricians in private practice in 1979 ($P < .001$) and, in 1984, more than the HLH ($P < .001$). The encounter distribution within the PCC in 1984 was not significantly different than in 1981 ($P > .05$).

The calculated index is displayed in Table 4 for each of the hospital clinics and times along with the mean index for the 20 private pediatric practitioners. The index for the PCC at both times was higher than the mean for Baltimore area pediatric practitioners (79.9).

Answers to the questions about re-

cency of care for PCC patients in 1981 were compared with answers for patients in the private practices. The percent reporting each type of care at the practice within a year is shown in Table 5. Compared with the patients attending sampled private pediatric practices in the Baltimore area in 1979, significantly more patients presenting for care at the PCC reported a "checkup" or cold/flu care at the practice in the past year.

COMMENT

Currently, standards for resident training in pediatric primary care, beyond continuity clinic time allotments specified by the Residency Review Committee, do not exist. This research was designed to evaluate one aspect of a particular primary care training site according to standards developed by the program staff. We believe a clinic organized to teach the practice of primary

care should provide primary care. Practitioners in other programs might find our method of characterizing the kind of care provided by our teaching practice useful.

The perhaps unexpected finding that the pediatric residents' continuity clinic at The Johns Hopkins Hospital had a high primary care index and provided more PC care than private pediatric practices in the area was encouraging, suggesting that the goal of providing a training site supportive of the attributes of primary care was being achieved in the two periods assessed. Particularly because the finding was unexpected, it is important to search for threats to the validity of the findings.

The primary care index is derived from parental reports of health service utilization as reflected in the answers to the questions posed on the patient log. Patients are known to be somewhat likely to offer what they perceive as the "socially desirable" or acquiescent response to questions about satisfaction with health care.¹⁶ The questions did not, however, address the question of satisfaction directly. Furthermore, we have no reason to believe that parents attending the PCC would be any more subject to this bias than would parents presenting to the HLH or, for that matter, to the area private practices. Likewise, there is no reason to suspect that one group of parents more than another would have difficulty accurately remembering the details of their children's health services. It is possible that our modest rephrasing of the questions to make them more appropriate to address to the parent of a patient made them easier to answer. This difference may help to explain why only 28 (3.5%) of 795 encounters in the PCC and HLH were not classifiable, while 11% of the 1409 encounters logged at the private pediatric practices could not be classified.¹⁴ Bias should be minimized by the fact that classifiable encounters were used as denominators for the calculations.

It is possible that the index is not the best measure of primary care for comparing pediatric practices. There is to date no generally accepted single measure of primary care, and currently used measures may produce divergent answers.³ The advantage of the index in

our situation was the availability of geographically relevant comparative data gathered at a not-too-distant time and the attractiveness of a previously validated measure of the health care process that could be easily applied.

An index score of 100 indicates that a physician or practice is providing only principal (or primary) care, while a score of 0 denotes a practice consisting entirely of CN care. While differences in scores were noted between the two Johns Hopkins clinics (Table 4), they were not as large as those previously reported between pediatrics and most specialties,¹⁸ and it is difficult to say what constitutes a "clinically" significant difference.

It is possible to mathematically compare the distributions of encounters among the four care categories for different service sites. Because a number of unmeasured changes may have influenced the process of health care provision in the Baltimore area over time, comparisons as close as possible in time deserve most credence. Therefore, only two-way statistical comparisons are made in Table 3: between the Baltimore area private practice results in 1979 and the PCC results obtained in the same season 2 years later; between data gathered simultaneously for PCC and HLH in 1984; and (only to assess stability of findings over years) between PCC data for 1981 and 1984.

Although the PCC in 1981 recorded a significantly larger proportion of encounters in the principal care category when compared with the private practice patient encounters, the similarity in percentages is certainly striking, adding weight to the conclusion that the PCC practice is representative of primary care if one considers private pediatric practice to be primary care. Also reassuring is the consistency in the index and the proportion of PC for the PCC in the two time periods. The fact that the index is lower and the proportion of PC care very different for the HLH when compared with the PCC suggests that the measures are sensitive enough to detect real differences in pediatric practices.

One possible source of bias in the encounter log data collection process is the circularity that only patients presenting to the practice are available for ques-

tioning; that is, fewer one-time patients who are going elsewhere for checkups and cold/flu care are being questioned. However, again, we have no reason to suspect that PCC patients would be more likely to leave the practice than patients of private practitioners. We know from other studies that the percentage of patients lost from the PCC practice over time is not large.¹⁶

Reports in the literature document how difficult it is for teaching practices to provide primary care. Breslau and Reeb⁶ studied provider continuity in their practice before and after they joined a medical school faculty and reorganized to become part of a university teaching clinic. Provider continuity for their sampled patients fell. Fletcher et al⁷ studied continuity and coordination of care for patients attending a hospital-based internal medicine teaching practice. Taking data from medical records, they found that 74.4% of visits made by the patients to the practice or elsewhere in the hospital were either "continuous" (to the principal provider) or "coordinated" (the principal provider knew of the visit to another provider and the second physician was aware of the primary provider). The authors were not satisfied with the percentage of visits to other providers that were coordinated by their definition, but did not present data by which coordination for the teaching practice patients could be compared with that afforded patients of private internists. Although our results are more encouraging, we did not study coordination or provider continuity.

Finally, analysis of recency of care reported by parents in the private practices in 1979 and the PCC in 1981 (Table 5) lends support to the assertion that the PCC practices primary care at a level similar to that of the private practices. The small differences noted in favor of the PCC might be explained by unmeasured differences in health care practices in the area over time, in the proportions of patients with chronic problems, or by the age profile of the two populations. Almost 12% of the patients in the private practices were age 15 years or older, compared with only about 4% of the PCC patients. In general, younger patients make more frequent, and therefore more recent, visits.

SUMMARY

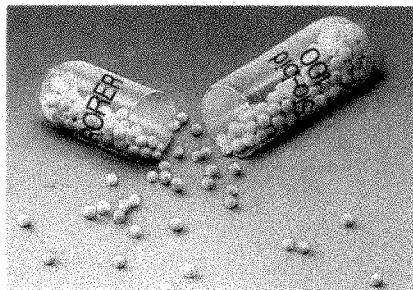
We believe our results suggest that a residents' continuity clinic can, and the PCC did at the times data were collected, provide primary care. Our study does not address the quality of that care, but we believe we have completed one of several desirable steps to confirm that a hospital pediatric outpatient clinic can be an appropriate primary care training site. We suggest that the primary care index may be a useful tool in the ongoing evaluation of a continuity teaching practice.

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Growing up on a steady theophylline is an open-and-shut case



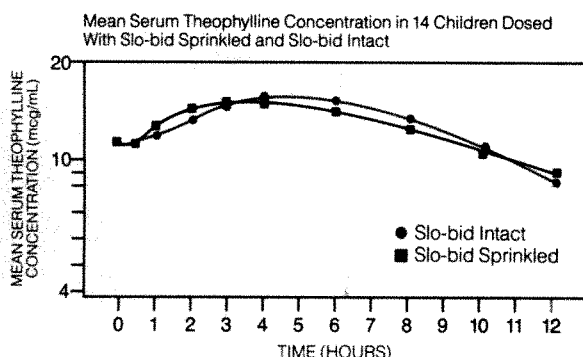
Sprinkled

Intact



Changing your patients from sprinkled to solid theophylline administration shouldn't mean changing their serum levels as well. With Slo-bid, you won't change a thing when your younger asthma patients are ready to switch to intact administration.

Slo-bid maintains steady theophylline levels when switching from sprinkled to solid administration¹



Switching from Slo-bid sprinkled to Slo-bid intact causes virtually no change in serum levels. Since the release system doesn't change, theophylline performance with both forms is identical. There's no need to restabilize your patients when they switch to taking capsules. In addition, capsules are the dosage form more patients prefer to take.²

Keep your patients' theophylline levels steady. Start and stay with Slo-bid. It's the perfect theophylline system for asthma patients to grow up with.

References: 1. Saccar CL, Gawchik S, Spitzer I, et al: Steady-state evaluation of sustained-release theophylline administered in apple-sauce in asthmatic children. *Immunol Allergy Pract* 1987;9:462-466.
2. Consumer attitudes toward solid forms of medication. Capsugel, Division of Warner-Lambert Company, March 1983.

In Asthma and Bronchitis



Slo-bid™

(theophylline, anhydrous)

Nothing beats our system

From the makers of **Azmacort™**
(triamcinolone acetonide)

Please see next page for brief summary of prescribing information.

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Slo-bid™

(theophylline, anhydrous)

50 mg, 75 mg, 100 mg, 125 mg, 200 mg, and 300 mg

Gyrocaps®

Timed-Release Capsules

BRIEF SUMMARY

DESCRIPTION: Slo-bid™ Gyrocaps® contain 50 mg, 75 mg, 100 mg, 125 mg, 200 mg, or 300 mg theophylline, anhydrous in the form of long-acting beads within a dye-free hard gelatin capsule and are intended for oral administration. Slo-bid Gyrocaps can be administered with a 12-hour dosing interval for a majority of patients and a 24-hour dosing interval for selected patients (see DOSAGE AND ADMINISTRATION section in full prescribing information for description of appropriate patient population).

INDICATIONS AND USAGE: For relief and/or prevention of symptoms from asthma and reversible bronchospasm associated with chronic bronchitis and emphysema.

CONTRAINDICATIONS: Slo-bid is contraindicated in individuals who have shown hypersensitivity to any of the components of this product. It is also contraindicated in patients with active peptic ulcer disease and in individuals with underlying seizure disorders (unless receiving appropriate anticonvulsant medication).

WARNINGS: Serum levels above 20 µg/mL are rarely found after appropriate administration of the recommended doses. However, in individuals in whom theophylline plasma clearance is reduced for any reason, even conventional doses may result in increased serum levels and potential toxicity. Reduced theophylline clearance has been documented in the following readily identifiable groups: 1) patients with impaired renal or liver function; 2) patients over 55 years of age, particularly males and those with chronic lung disease; 3) those with cardiac failure from any cause; 4) patients taking oral contraceptives; 5) neonates and infants under 1 year of age; and 6) those patients taking certain drugs (see PRECAUTIONS, Drug Interactions). Frequently, such patients have markedly prolonged theophylline serum levels following discontinuation of the drug.

Reduction of dosage and laboratory monitoring is especially appropriate in the above individuals.

Serious side effects such as ventricular arrhythmias, convulsions, or even death may appear as the first sign of toxicity without any previous warning. Less serious signs of theophylline toxicity (i.e., nausea and restlessness) may occur frequently when initiating therapy but are usually transient; when such signs are persistent during maintenance therapy, they are often associated with serum concentrations above 20 µg/mL. Stated differently, *serious toxicity is not reliably preceded by less severe side effects.* A serum concentration measurement is the only reliable method of identifying a potential for life-threatening toxicity.

Many patients who require theophylline exhibit tachycardia due to their underlying disease process, so the cause/effect relationship to elevated serum theophylline concentrations may not be appreciated.

Theophylline products may cause dysrhythmia and/or worsen preexisting arrhythmias and any significant change in rate and/or rhythm warrants monitoring and further investigation.

Studies in laboratory animals (minipigs, rodents, and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

PRECAUTIONS: **General:** On the average, theophylline half-life is shorter in cigarette and marijuana smokers than in nonsmokers, but smokers can have half-lives as long as nonsmokers. Theophylline should not be administered concurrently with other xanthine preparations. Use with caution in patients with hypoxemia, hypertension or with a history of peptic ulcer. Theophylline may occasionally act as a local irritant to the GI tract, although GI symptoms are more commonly centrally mediated and associated with serum drug concentrations over 20 µg/mL.

Information for Patients:

The physician should reinforce the importance of taking only the prescribed dose at the prescribed time intervals. The patient should alert the physician if symptoms occur repeatedly especially near the end of a dosing interval. When prescribing administration by the sprinkle method, details of the proper technique should be explained to the patient.

Laboratory Test: Serum levels should be monitored periodically to determine the theophylline levels associated with observed clinical response and to identify the potential for toxicity. For such measurements, the serum sample should be obtained at the time of peak concentration, approximately 5-9 hours after the morning dose. It is important that the patient has not missed or taken additional doses during the previous 48 hours and that dosing intervals have been reasonably equally spaced.

DOSE ADJUSTMENT BASED ON SERUM THEOPHYLLINE MEASUREMENTS WHEN THESE INSTRUCTIONS HAVE NOT BEEN FOLLOWED MAY RESULT IN RECOMMENDATIONS THAT PRESENT RISK OF TOXICITY TO THE PATIENT.

Drug Interactions:

Drug-Drug: Toxic synergism with ephedrine has been documented and may occur with some other sympathomimetic bronchodilators. In addition, the following drug interactions have been demonstrated:

Theophylline with:	Increased serum theophylline levels
Allopurinol (high dose)	Increased serum theophylline levels
Cimetidine	Increased serum theophylline levels
Erythromycin, Troleandomycin	Increased renal excretion of lithium
Lithium carbonate	Increased serum theophylline levels
Oral contraceptives	Decreased theophylline and phenytoin serum levels
Phenytoin	Decreased serum theophylline levels
Rifampin	

Drug-Food: Taking Slo-bid immediately after a high-fat content meal such as 8 ounces whole milk, 2 fried eggs, 2 strips bacon, one bran muffin with butter, 2 ounces hash brown potatoes (about 789 calories, including approximately 49 gm of fat) may result in a decrease in the rate of absorption, but with no significant difference in the extent of absorption (see CLINICAL PHARMACOLOGY Pharmacokinetics). The influence of the type and amount of other foods, as well as the time interval between drug and food, has not been studied.

Drug/Laboratory Test Interactions: Currently available analytic methods, including high-pressure liquid chromatography and immunoassay techniques, for measuring serum theophylline levels are specific. Metabolites and other drugs generally do not affect the results. Other new analytic methods are also now in use. The physician should be aware of the laboratory method used and whether other drugs will interfere with the assay for theophylline.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies have not been performed with theophylline.

Chromosome-breaking activity was detected in human cell cultures at concentrations of theophylline up to 50 times the therapeutic serum concentrations in humans. Theophylline was not mutagenic in the dominant lethal assay in male mice given theophylline intraperitoneally in doses up to 30 times the maximum daily human oral dose.

Studies to determine the effect on fertility have not been performed with theophylline.

Pregnancy: Pregnancy Category C—Animal reproduction studies have not been conducted with theophylline. It is also not known whether theophylline can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Theophylline should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Theophylline is distributed into breast milk and may cause irritability or other signs of toxicity in nursing infants. Because of the potential for serious adverse reactions in nursing infants from theophylline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:

Safety and effectiveness of Slo-bid Gyrocaps administered:

1. Every 24 hours in children under 12 years of age, have not been established.
2. Every 12 hours in children under 6 years of age, have not been established.

ADVERSE REACTIONS: The following adverse reactions have been observed, but there has not been enough systematic collection of data to support an estimate of their frequency. The most consistent adverse reactions are usually due to overdosage.

Gastrointestinal: nausea, vomiting, epigastric pain, hematemesis, diarrhea.

Central Nervous System: headaches, irritability, restlessness, insomnia, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions.

Cardiovascular: palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, ventricular arrhythmias.

Respiratory: tachypnea

Renal: potentiation of diuresis.

Other: alopecia, hyperglycemia, inappropriate ADH syndrome, rash.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription. Keep this and all medications out of the reach of children.

HOW SUPPLIED: Slo-bid Gyrocaps are identified as follows:

- 50 mg—Clear (cap) and opaque white (body) capsule with 50 printed in red
- 75 mg—Opaque white (cap) and clear (body) capsule with 75 printed in red
- 100 mg—Clear capsule with 100 printed in red
- 125 mg—Opaque white (cap) and opaque white (body) capsule with 125 printed in red
- 200 mg—Opaque white (cap) and clear (body) capsule with 200 printed in red
- 300 mg—Opaque white capsule with 300 printed in red

Slo-bid Gyrocaps 50 mg are available in bottles of 100 (NDC 0075-0057-00), bottles of 1000 (NDC 0075-0057-99) and in unit dose 10 x 10 (NDC 0075-0057-62). Slo-bid Gyrocaps 75 mg are available in bottles of 100 (NDC 0075-1075-00), bottles of 1000 (NDC 0075-1075-99) and in unit dose 10 x 10 (NDC 0075-0057-62). Slo-bid Gyrocaps 100 mg are available in bottles of 100 (NDC 0075-0100-00), bottles of 1000 (NDC 0075-0100-99) and in unit dose 10 x 10 (NDC 0075-0100-62). Slo-bid Gyrocaps 125 mg are available in bottles of 100 (NDC 0075-1125-00), bottles of 1000 (NDC 0075-1125-99) and in unit dose 10 x 10 (NDC 0075-1125-62). Slo-bid Gyrocaps 200 mg are available in bottles of 100 (NDC 0075-0200-00), bottles of 1000 (NDC 0075-0200-99) and in unit dose 10 x 10 (NDC 0075-0200-62), and Slo-bid Gyrocaps 300 mg are available in bottles of 100 (NDC 0075-0300-00), bottles of 1000 (NDC 0075-0300-99) and in unit dose 10 x 10 (NDC 0075-0300-62), and are manufactured by

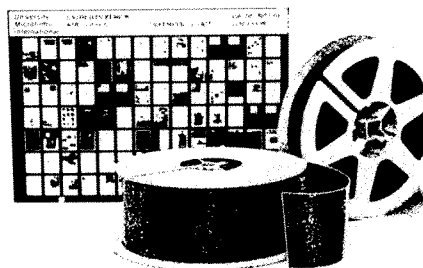
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Late Sudden Unexpected Deaths in Hospitalized Infants With Bronchopulmonary Dysplasia

Steven H. Abman, MD; Molly F. Burchell, MD; Michael S. Schaffer, MD; Adam A. Rosenberg, MD

• To determine the relative contribution of sudden death as a cause of late inpatient mortality in newborns after prolonged mechanical ventilation, we reviewed the charts of 348 patients who received ventilation assistance and who were admitted to the neonatal intensive care unit during a 26-month period. The overall mortality rate for these patients was 25%, with 88% (77/88) of these deaths occurring within 30 days of birth. Eleven infants died after more than 60 days of mechanical ventilation. Seven of these late deaths were sudden, unexpected in-hospital deaths. Sudden deaths occurred at a mean (uncorrected) age of 12 months (range, 4 to 27 months), during periods when infants appeared to be stable or clinically improving, were unrelated to recent respiratory exacerbations, and occurred despite prompt resuscitative efforts. Four infants still required mechanical ventilation, and 4 had tracheostomies at the time of death. All of the infants had chronic hypercarbia (>50 mm Hg) and an elevated serum bicarbonate level (>30 mmol/L), but not hyponatremia, hypochloremia (<80 mmol/L), or alkalemia. Left and right ventricular hypertrophy, multiple drug therapy, recurrent cyanotic episodes, and frequent unexplained fevers were common. In comparison with 17 bronchopulmonary dysplasia survivors who required longer than 60 days of ventilation therapy, the late deaths group more frequently had left ventricular hypertrophy and received prolonged combination theophylline anhydrous and β -adrenergic agonist therapy. We report that sudden death can occur in infants with severe bronchopulmonary dysplasia despite in-hospital cardiopulmonary monitoring and the rapid institution of cardiopulmonary resuscitation, and is a significant cause of late mortality in infants who receive ventilation therapy for longer than 2 months.

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Bronchopulmonary dysplasia (BPD) represents a spectrum of persistent cardiopulmonary abnormalities following oxygen and ventilator therapy for neonatal respiratory failure.^{1,2} Although the clinical course for most infants with BPD is characterized by steady improvement in growth, lung function, and oxygen requirement, a significant proportion of neonatal intensive care unit (NICU) survivors with BPD have major morbidity and mortality.^{2,4} Causes of mortality in infants with BPD include progressive cardiorespiratory failure, sepsis, pneumonia, and sudden death.^{2,7-16} Although sudden deaths have been previously reported in infants with BPD, causes and associated risk factors are unknown.^{10,12,15} In addition, previous reports have described sudden death exclusively in outpatient populations of infants with BPD.^{10,13,15} We have observed late sudden deaths in hospitalized children with BPD, who were clinically stable or improving in the period preceding death. To determine the relative contribution of these sudden, unexpected deaths to the late mortality of severe BPD and to initiate investigation into potential risk factors, we reviewed the clinical courses of children with late deaths following long-term ventilator support in the NICU.

PATIENTS AND METHODS

We reviewed the hospital records of all ventilated newborns admitted to the NICU at the University of Colorado, Denver, between June 1984 and August 1986. By chart review, we determined the period of death as less than 30 days of age, between 30 and 60 days, between 60 and 90 days, or 91 days or more. Records of infants dying after more than 60 days of mechanical support were analyzed for details of their clinical course. The following data were recorded: birth weight, gestational age, associated perinatal problems, primary diagnosis when admitted to the NICU, duration of mechanical ventilation, and associated clinical problems (eg, apnea, recurrent cyanotic episodes, frequent fevers, structural airway abnormalities, cardiac hypertrophy, systemic hypertension,

intraventricular hemorrhage, hydrocephalus, and seizures). The types and duration of medications used, serum electrolyte levels, blood gas tensions, and outcome were also recorded.

Recurrent cyanotic episodes were defined as frequent episodes of sudden onset of severe cyanosis, with or without subsequent bradycardia and recognized as clinically significant, as reflected by such interventions as hand-bagging, calming, sedation, or the administration of β -adrenergic medications. Recurrent fever was defined as sustained or frequent elevations of temperature above 38.5°C without apparent source. Systemic hypertension was defined as persistent systolic blood pressure above 113 mm Hg on repeated assessments obtained while the patient was at rest.¹⁷ Serum electrolyte disturbances were defined as persistent abnormalities throughout the hospital course or within 2 weeks of death. Abnormal measurements included values of serum sodium less than 130 mmol/L, serum potassium less than 3.5 mmol/L, serum chloride less than 80 mmol/L, serum bicarbonate greater than 30 mmol/L, and PaCO_2 over 50 mm Hg. Growth parameters were assessed according to percentile for corrected age, using National Center for Health Statistics standards. Echocardiographic and electrocardiographic (ECG) measurements were compared with age-appropriate normal values.^{18,19}

Clinical management was determined by the NICU and pediatric special care unit medical teams managing the individual patients. Despite some variations in therapeutic approaches, respiratory care included maintaining oxygen saturations or transcutaneous PCO_2 consistently above 92% to 94% or 55 mm Hg while the infant was awake, feeding, or asleep as previously described.⁴ Arterial PCO_2 was allowed to remain between 50 and 65 mm Hg as long as pH was maintained in the normal range (7.35 to 7.45). Medications often used in the management of these children with chronic lung disease included diuretics (furosemide or a combination of hydrochlorothiazide and spironolactone [Aldactone]), β -adrenergic nebulizers, theophylline, and corticosteroids. Other aspects of clinical care for these infants was similar to those recently described by Schreiner et al.¹²

Comparisons of the clinical and laboratory courses were made between a control group of infants with severe BPD who required

longer than 60 days of mechanical ventilation who survived (group 1) and the infants with BPD who died suddenly (group 2). Twenty-three of the 34 infants with BPD who received ventilatory assistance for longer than 60 days survived. Of these, 4 patients required long-term ventilator support to treat severe tracheomalacia (3 children) or an upper airway obstruction due to a massive encephalocele (1 infant). One infant with severe congestive heart failure due to congenital heart disease was ventilated. Because these children had minimal clinical and radiologic signs of lung parenchymal disease, they were excluded from further comparisons with the infants with BPD. A sixth infant had chronic lung disease following long-term ventilation but was born with a severe hypertrophic cardiomyopathy and was therefore excluded. The hospital records of the remaining 17 infants with clinical BPD and parenchymal disease (group 1) were reviewed as described earlier.

Statistical analysis was performed by Student's *t* test and Fisher's Exact Test with a *P* < .05 considered significant.

RESULTS

We identified 348 infants who required mechanical ventilation therapy in our NICU during this 26-month period. As shown in Table 1, 88 infants died (25.3% mortality), with 77 deaths (88%) occurring in infants ventilated for less than 30 days. All of the infants who were ventilated for 30 to 60 days survived. Of 34 infants ventilated beyond 60 days, 11 died (32%), with all of these deaths occurring beyond 90 days. Seven of these deaths were sudden and unexpected. Causes of death in the 4 other infants were perforated duodenal ulcer during long-term corticosteroid therapy, progressive respiratory failure in a 24-week preterm infant and in an infant with congenital diaphragmatic hernia, and severe cardiac failure in an infant with cutis laxa and an aneurysm of the ascending aorta.

Table 2 gives some of the clinical characteristics of the seven infants with BPD who died suddenly. Mean birth weight and gestational age were 1184 g (range, 790 to 2000 g) and 28 weeks (range, 26 to 33 weeks), respectively. The primary diagnosis when admitted to the NICU was hyaline membrane disease for all of the infants. Only one had an intraventricular hemorrhage of grade 2 or above. Mean age at the time of death was 12.3 months (uncorrected),

Days Ventilated	Survivors	Deaths	Mortality Rate, %
<30	207	77	27.6
30-60	30	0	0
60-90	15	2	11.8
>90	8	9	52.5
Total	260	88	25.3

Parameter*	Group		P†
	1 (n = 17)	2 (n = 7)	
Gestational age, wk‡	26.5 ± 1.3	23.4 ± 2.2	<.01
Birth weight, g‡	862 ± 199	1184 ± 398	<.02
Duration PPV, mo‡	3.1 ± 2.3	3.6 ± 8.4	<.02
Associated clinical problems			
<3rd percentile			
Weight	13/17	4/7	NS
OFC	4/17	3/7	NS
Systemic hypertension	1/17	3/7	NS
Ventricular hypertrophy			
L	2/17	7/7	<.001
R	8/17	6/7	NS
Recurrent cyanotic episodes	5/17	6/7	<.02
Tracheostomy	2/17	4/7	<.04
Chronic therapy with theophylline and 3-adrenergic agonist	1/17	6/7	<.001
Chronic diuretic therapy	11/17	7/7	NS

*PPV indicates positive pressure ventilation; OFC, occipital frontal circumference.

†P value compares groups 1 and 2 by Student's *t* test or Fisher's Exact Test. NS indicates not significant.

‡Values expressed as mean ± SD.

ranging between 4 and 27 months. At the time of death, four infants (57%) still required mechanical ventilation therapy and four had tracheostomies. Five of the seven infants had at least one bronchoscopy, with abnormalities reported in three patients. These included tracheomalacia (two infants), subglottic stenosis (one infant), and bronchial stenosis (two infants). Each child was clinically stable or steadily improving preceding sudden death. One infant died within days of a date set for home discharge. None had evidence of acute respiratory tract infection, or required an increase in the frequency or dosage of diuretic or bronchodilator therapy in the week preceding death. None of the infants had elevated theophylline levels (>20 mg/L). Although six infants had

Paco₂ above 50 mm Hg and all infants had serum bicarbonate levels greater than 30 mmol/L, none had significant hypochloremia (<80 mmol/L). All seven infants had left ventricular hypertrophy (LVH). The diagnosis of LVH was made by ECG and echocardiogram in two patients, echocardiogram only (with normal ECG studies) in four infants, and at autopsy only in one child who had several normal ECG studies without an echocardiogram. Late echocardiographic studies were performed in six infants, at a mean age of 18.6 months. All six children had evidence of LVH, as determined by increased left ventricular posterior wall and interventricular septal thickness. Left ventricular internal diameter was decreased in four of six patients. In addition, right ventricular

systolic time interval was elevated in five of six infants.

In each case, at the time of death, a sudden onset of bradycardia was noted, which persisted and progressed to asystole and death, despite the rapid institution of cardiopulmonary resuscitation. None of the patients had evidence of plugged endotracheal or tracheostomy tubes, or improved with reintubation. Death ensued despite ventilation by hand-bagging with 100% fraction of inspired oxygen concentration chest compression and the administration of cardiotonic medications. Autopsies were obtained in four infants, but failed to document a specific cause of death. Postmortem bacterial or viral cultures failed to demonstrate bacteremia, pneumonia, or other infections. Autopsy findings included biventricular hypertrophy with mild intercellular edema without histologic evidence of acute myocardial infarction (four infants). One infant had endocardial fibroelastosis. Old myocardial infarction or inflammatory infiltrates were not found. The cardiac conduction system was not examined. Mild pulmonary hypertensive changes, consisting predominantly of smooth-muscle thickening, were found in each case. Findings diagnostic of pneumonia or aspiration were absent. Acute hemorrhage, thrombosis, or recent ischemic brain injury was not noted. Chronic neuropathologic lesions included periventricular leukomalacia (two infants) and severe micropolygyria with scaphocephaly and hydrocephalus ex vacuo (one infant).

To identify clinical risk factors potentially associated with these deaths, we compared the clinical and laboratory findings of infants with BPD who died suddenly (group 2, Table 2) with a control group of infants with BPD who survived after prolonged ventilation therapy (>2 months, group 1). In comparison with control infants, the sudden death group had significantly greater gestational age ($P<.01$) and birth weight ($P<.02$) and required longer ventilator support ($P<.02$). In addition, the presence of LVH, recurrent cyanotic episodes, tracheostomy, and long-term combination drug therapy of theophylline with β -nebulizer were more frequent in group 2 infants. Persistent electrolyte abnormalities, including low

serum concentrations of sodium, potassium, and chloride, or alkalemia, were infrequently found in either group. The incidence of nephrocalcinosis and grade 2 or greater intraventricular hemorrhage were similar between groups.

To further examine clinical factors that may be associated with late sudden deaths, we also compared the sudden death group with the five surviving infants with BPD in group 1 who were ventilated for more than 90 days. These five infants were more comparable with the group 2 infants in terms of the severity of their hospital courses. No significant differences were found between these groups in gestational age (26.6 ± 2.0 weeks for survivors [mean \pm SD]), birth weight (848 ± 305 g [mean \pm SD]), weight below the third percentile (three of five patients), systemic hypertension (one of five patients), right ventricular hypertrophy (three of five patients), or tracheostomy (two of five patients). The frequency of recurrent cyanotic episodes and frequent unexplained fevers were similar between groups. However, the infants with BPD who died suddenly had a significantly greater incidence of LVH (one of five vs seven of seven patients; $P<.02$) and were more frequently treated with the combination of theophylline and β -adrenergic medications (one of five vs six of seven patients; $P<.05$). Long-term use of theophylline, β -agonist or diuretic therapies alone, or the combination of diuretic with either theophylline or β -agonist were not different among the groups. All patients from both groups received diuretic therapy.

COMMENT

We report a previously unpublished observation that infants with BPD can die suddenly and unexpectedly as inpatients, despite cardiorespiratory monitoring and the rapid initiation of aggressive cardiopulmonary resuscitation. Sudden unexpected deaths occurred in 7 of the 11 late deaths in infants with severe BPD who had been treated with mechanical ventilation for more than 60 days. These in-hospital deaths occurred despite stable or improving clinical status, without apparent acute respiratory exacerbation, and despite the rapid initiation of resuscitation efforts. Death was preceded by the acute onset of bra-

dycardia, leading to asystole that was unresponsive to cardiopulmonary resuscitation, including the use of cardiotonic medications. These sudden deaths occurred in infants with BPD who had common manifestations of severe disease, including prolonged mechanical ventilator support, multiple drug therapy, persistent LVH and right ventricular hypertrophy, and prolonged hospitalization. In addition, recurrent cyanotic "spells" and multiple episodes of unexplained fevers were common. Despite the presence of these chronic clinical problems, these sudden deaths are of undetermined etiology and occurred when the patients appeared clinically stable. When compared with survivors of long-term mechanical ventilation therapy following NICU admission during the same period, the sudden death group more frequently had LVH and were more often receiving concomitant diuretic, β -adrenergic, and theophylline therapy. Study groups, however, were small, and the true incidence of LVH may be underestimated in the survivors.

Previous studies that have addressed inpatient deaths in older infants with severe BPD have not reported sudden death.^{11,12,14,16} Progressive respiratory failure, heart failure, airway accidents, sepsis, and infection were most commonly found. In contrast to one study of late mortality in BPD,¹¹ we did not find an association with chloride deficiency or alkalemia with these deaths. As was the case in a recent report of infants with BPD dying following prolonged ventilation therapy, we observed that recurrent cyanotic episodes are common in the infants with BPD who died suddenly.¹⁶ However, these spells are also frequently present in many survivors of severe BPD.

An increased incidence of sudden deaths in infants with chronic lung disease following discharge from the NICU has been previously described.^{10,13,16} Werthammer et al¹⁰ reported that 11% of the infants with BPD who died of "sudden infant death syndrome" (SIDS) following discharge from the NICU. In comparison, the incidence of SIDS in preterm infants without BPD was 1.5%. However, considering the cardiopulmonary abnormalities associated with BPD, it seems inappro-

priate to classify unexplained sudden deaths in this population as SIDS.²⁰ Two other studies found that sudden deaths accounted for 10% and 28% of late deaths following discharge from the NICU.^{13,15} In these reports, however, sufficient clinical data are not provided to assess the presence or severity of cardiopulmonary disease in the sudden deaths. Most of the reported sudden deaths were in young outpatients, younger than 4 months of age. In contrast, we have previously noted that sudden deaths in infants with BPD who were enrolled in our home oxygen follow-up (outpatient) program are rare.^{4,21} Reports of sudden deaths in outpatient infants with BPD have led to the suggestion that aggressive monitoring, close follow-up, and early cardiopulmonary resuscitation can prevent these deaths.^{22,23} The cases in our report suggest that sudden deaths in BPD can occur despite monitoring and the early intervention. In addition, these findings imply that mechanisms, in addition to abnormal control of breathing or plugged tracheostomy tubes, may contribute to sudden death in BPD.

Left ventricular hypertrophy was present in each of the infants with BPD who died suddenly. Whether the development or presence of persistent LVH in infants with BPD is a risk factor or simply parallels more severe disease warrants prospective study. Left ventricular hypertrophy has been previously reported in infants with BPD, but its cause and potential contribution to the late mortality of BPD, including sudden death, are unclear.⁹ A high incidence of LVH (14 of 28 cases) was also found at autopsy in a previous study of late BPD deaths,⁸ but was rarely found in previous clinical studies of late mortality in infants with BPD.^{11,16} Of clinical importance is the finding in this study that five of the seven infants with LVH determined by echocardiogram and autopsy had serial ECG studies without evidence of LVH, suggesting that the incidence of LVH may be underreported if only ECG assessments are performed at follow-up. The etiology of LVH in infants with BPD is unknown. Although systemic hypertension can be associated with LVH in infants with BPD,²⁴ many infants with BPD who have LVH do not have recognized ele-

vations of blood pressure. Other potential causes of LVH include the effects of ventricular interdependence,²⁵ repeated episodes of ischemic myocardial injury,^{14,26,27} or myocardial toxicity from aggressive bronchodilator or corticosteroid therapy. Chronic adrenergic stimulation from aggressive diuretic use with volume contraction, hypercapnia, stress, or diminished pulmonary vascular clearance or net production of norepinephrine are additional possibilities.²⁸⁻³²

Although acute respiratory infection is a possible contributing factor to death, the lack of prodromal signs in these sudden death cases and the negative results of postmortem bacterial and viral cultures make it less likely as a cause of death in these cases. Although it has been speculated that late sudden deaths may reflect abnormalities in the control of breathing or airway obstruction,¹⁰ the inpatient deaths reported herein suggest that alternative mechanisms may also be important. Acute airway obstruction seems an unlikely cause because of the rapid resuscitation response, which included assessment for airway obstruction, and the immediate initiation of ventilation. However, it is possible that acute hypoxia, triggered by transient airway obstruction, apnea, severe gastroesophageal reflux, or other events, can precipitate a dysrhythmia, which proves fatal, despite resolution of the hypoxia.³³ In addition, myocardial hypertrophy increases the risk for sudden death and dysrhythmias, especially secondary to elevations of catecholamine levels.^{34,35} Dramatic surges of plasma catecholamine levels can occur during cyanotic episodes in infants with BPD.³⁰ Hypoxia, hypokalemia, viral infection, and other factors may also potentially aggravate the risk for dysrhythmias in this clinical setting.³⁴ Whether methylxanthines and adrenergic agonists used to treat BPD contribute to an increased risk of sudden death is unknown. It has been speculated that the recently recognized rise in asthma deaths may in part be related to increasing use of combined theophylline and β -adrenergic agonists.³⁶

Although neurologic abnormalities could potentially contribute to sudden death, no evidence of an acute catastrophic event (eg, acute hemorrhagic

or ischemic brain injuries) was found. Although chronic neuropathologic lesions, including periventricular leukomalacia and severe micropolygyria with scaphocephaly and hydrocephalus ex vacuo, were observed, the exact mechanisms by which these lesions could contribute to the sudden demise of these hospitalized patients with BPD is unclear. However, the number of autopsies were limited to four children, and future investigations of the potential role of neurologic abnormalities to sudden death are needed before firm conclusions can be made.

CONCLUSION

We conclude that sudden unexpected late deaths contribute significantly to late mortality in older infants with severe BPD following prolonged mechanical ventilation. That mortality is high in sick children with BPD who require prolonged ventilation is not surprising. However, although these infants died with BPD, the actual cause of death is unknown, and mechanisms underlying the sudden nature of their death, especially while appearing to be clinically stable or improving, are unclear. Whether cardiac hypertrophy or our current use of "polypharmacy"³⁹ in the management of severe BPD contributes to sudden death or related clinical morbidity remains to be determined. Although this study is limited by its retrospective nature, it describes a substantial clinical problem and will, it is hoped, serve to stimulate future prospective studies of factors that contribute to late mortality and sudden death in infants with severe BPD.

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In Other AMA Journals

ARCHIVES OF DERMATOLOGY

Photosensitizing Potential of Certain Nonsteroidal Anti-Inflammatory Drugs

Kays H. Kaidbey, MD; Fred N. Mitchell, MD (*Arch Dermatol*. 1989;125:783-786)

Phototoxicity of Nonsteroidal Inflammatory Drugs: Coincidence or Specific Mechanism?

Irene E. Kochevar, PhD (*Arch Dermatol*. 1989;125:824-826)

Height and Weight Following Lead Poisoning in Childhood

Henrietta K. Sachs, MD, Donald I. Moel, MD

• The effect of lead on growth was examined in 104 lead-poisoned subjects (Pb-B [blood lead concentration], 4.82 to 22.73 $\mu\text{mol/L}$) and 27 sib-controls (Pb-B, 0.48 to 1.88 $\mu\text{mol/L}$). Blood lead concentration, height, and weight are reported for 1974 (the year of their first posttreatment recall for evaluation) and for 1985 (the year of their sixth recall). In 1974, when their mean age was 8 years and their mean Pb-B was 1.68 $\mu\text{mol/L}$, about 70% of the patients and sib-controls were in the 50th to 95th percentiles for height and weight. In 1985, when their mean age was 18 years and all Pb-Bs were less than 1.20 $\mu\text{mol/L}$, height and weight percentiles were similar to those of 1974. Lead did not seem to affect the genetic predisposition for height attainment, at high or low blood lead levels. (AJDC. 1989;143:820-822)

Blood lead concentration (Pb-B) at low levels has been cited as causing several disparate conditions in children, among them, growth retardation.¹ To test the accuracy of this observation, we examined the height and weight data of lead-poisoned patients (Pb-B, 4.82 to 22.73 $\mu\text{mol/L}$) and a sibling cohort (Pb-B, 0.48 to 1.88 $\mu\text{mol/L}$) whom we have followed up for 15 to 20 years. The first recall was in 1974, 2 to 6 years after the patient-sib was treated; the sixth recall was in 1985, when all subjects but one were adolescents or adults.

SUBJECTS AND METHODS

Patients and sib-controls have been described.² They were found through a broad, urban screening program. Patients, who were 16 to 55 months of age when lead poisoning was diagnosed, were treated with British anti-Lewisite and edetic acid, or edetic acid alone, then with penicillamine until Pb-B fell to 2.41 $\mu\text{mol/L}$. Blood lead was then permit-

ted to fall spontaneously to normal adult levels, a process that often extended beyond pubescence.³ A report describing the patients' present psychosocial function is being prepared and will not be presented herein. Sib-controls did not have pica or a Pb-B above 1.88 $\mu\text{mol/L}$, the requisite blood level for evaluation between 1966 and 1972, when all subjects were screened, and the patient cohort was treated.

Data were obtained from 104 patients and 27 sib-controls in 1974, and from 77 patients and 21 sib-controls in 1985. Height and weight measurements were tabulated according to percentiles of the National Center for Health Statistics.⁴ Subjects were placed in the following four categories, based on pretreatment Pb-B: 9.62 $\mu\text{mol/L}$ or more; 7.23 to 9.60 $\mu\text{mol/L}$; 4.82 to 7.19 $\mu\text{mol/L}$; and sib-controls, 1.88 $\mu\text{mol/L}$ or less. The number of measurements in or above the 50th percentile for height (Ht%) and for weight (Wt%) for the 2 recall years are given in Table 1.

RESULTS

Initial Pb-B Was Not a Factor Contributing to Growth Retardation

In 1974, 73 patients had Pb-Bs of 1.44 to 2.75 $\mu\text{mol/L}$ and 30 had Pb-Bs of 0.62 to 1.88 $\mu\text{mol/L}$; 51 (70%) of the higher lead group and 23 (77%) of the lower group were in or above the 50th Ht% (Table 1). By 1985, when almost all subjects had completed the adolescent growth spurt, and all Pb-Bs were less than 1.30 $\mu\text{mol/L}$, 53 (69%) of the 77 patients were in or above the 50th Ht%, and 65 (84%) were in or above the 50th Wt% (Table 1).

Symptomatic Lead Poisoning Was Not a Factor

Twenty of the 32 symptomatic patients were in or above the 50th Ht% at both recalls. The three children who had at least one seizure were in the 3rd, 50th, and 95th Ht%, respectively.

Age at Onset Was Not a Factor

In 1974, 44 patients were between 3 and 6 years of age, and closest in time to their episode of lead poisoning; 28 (64%) of the 44 were in or above the 50th Ht% and Wt%. Ten of the 13 youngest patients (77%), aged 3 and 4 years, were in or above the 50th Ht%, compared with 18 (58%) of 31 patients, aged 5 and 6 years (Table 2).

Ethnicity Was a Determinant of Height

All subjects were black or Hispanic. Seven of the eight Hispanic patients were in the first to the 25th Ht%, and six were in the first to the 25th Wt%. Eight of an additional nine Hispanics whose Pb-Bs were below 4.82 $\mu\text{mol/L}$ and two of their three sib-controls were below the 35th Ht%. In 1974, the eight Hispanics (Pb-B, $\geq 4.82 \mu\text{mol/L}$) had a mean Ht% of 16, and a mean Wt% of 38. The six Hispanics available in 1985 had a mean Ht% of 21 and a mean Wt% of 37. In both follow-up years, 20% of the patients, including most of the Hispanics, were in or below the 16th Ht%, and 28% (none of them Hispanics) were in or above the 84th Ht%.

Heredity Was the Determinant of Height

In 1974, 27 patients provided a sib-control cohort. Concordance between siblings for height percentiles was present in 15 pairs (56%); 4 patients were in a higher percentile than their sibs (15%), and 8 were in a lower one (30%). Concordance for weight percentiles was similar in 1985, as were the results (Table 3). To eliminate the role of chance in concordance, sets were rearranged so that patient 1 was paired to sib-control 2, etc, and patient 27 to sib-control 1. Only 8 patients (30%) exhibited concordance for height; 10 patients were taller and 10

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Table 1.—Height and Weight in the 50th Percentile or Above for Subjects With Blood Lead Concentrations of 4.82 $\mu\text{mol/L}$ or More Treated Between 1966 and 1972*

Maximum Pb-B, $\mu\text{mol/L}$ Pretreatment	No. of Subjects	Mean Pb-B, $\mu\text{mol/L}$ in 1974 (Range)	Mean Age, y (Range)	No. (%) in the 50th Percentile or Above	
				Ht	Wt
1974 Recall (N = 104)					
9.65-22.73	14	1.83 (1.30-2.50)	8 (4-11)	10 (71)	11 (79)
7.23-9.60	28	1.68 (0.86-2.55)	7 (3-12)	17 (61)	17 (61)
4.82-7.19	62	1.64 (0.62-2.41)	8 (3-12)	48 (77)	52 (84)
<1.93†	27	0.82 (0.57-1.54)	9 (4-16)	20 (74)	16 (59)
1985 Recall (N = 77)					
9.65-22.73	13	0.62 (0.48-0.96)	18 (15-22)	8 (62)	10 (75)
7.23-9.60	23	0.57 (0.48-1.10)	18 (15-20)	16 (70)	19 (83)
4.82-7.19	41	0.57 (0.48-1.20)	18 (9-23)‡	29 (71)	36 (88)
<1.93†	21	0.57 (0.48-1.10)	17 (13-23)	17 (81)	15 (71)

*Pb-B indicates blood lead concentration; Ht, height; and Wt, weight.

†Sib-controls.

‡One child, cousin to two patients, entered the study in 1980 at his mother's request. He was treated for lead poisoning at Cook County (Illinois) Hospital in 1977.

Table 2.—Height and Weight in the 50th Percentile or Above of Subjects Aged 3 to 6 Years at 1974 Recall*

Mean Maximum Pb-B, $\mu\text{mol/L}$ (Range)	No. of Subjects	Age, y	Mean Pb-B, $\mu\text{mol/L}$ in 1974 (Range)	No. (%) in the 50th Percentile or Above	
				Ht	Wt
7.38 (4.92-11.0)	13	3 and 4	1.78 (1.45-2.42)	10 (77)	9 (69)
6.41 (4.82-10.47)	18	5	1.73 (0.92-2.51)	11 (61)	10 (56)
7.82 (4.82-22.73)	13	6	1.59 (0.82-2.56)	7 (54)	9 (69)

*These subjects had blood lead concentrations (Pb-Bs) of 4.82 $\mu\text{mol/L}$ or more. Ht indicates height; and Wt, weight.

Table 3.—Comparison of Height and Weight Percentiles of Patient to Sib-Controls

Year	No. of Pairs	Height Percentiles, No. (%)			Weight Percentiles, No. (%)		
		Patient = Sib- Control	Patient > Sib- Control	Patient < Sib- Control	Patient = Sib- Control	Patient > Sib- Control	Patient < Sib- Control
1974	27	15 (56)	4 (15)	8 (30)	14 (53)	9 (33)	4 (15)
1985	17	10 (59)	2 (12)	5 (29)	9 (53)	4 (24)	4 (24)

patients were shorter than the nonrelated sib-control.

COMMENT

There are few published observations on the association of growth with Pb-B. Absence of effect may be surmised from lack of reference to interference with development in environmentally exposed children^{5,6} examined for medical and neurological lesions.

Reports of impaired growth have been derived from data collected for other objectives. While investigating dietary intake, Mooty et al⁷ obtained a Ht% mean of 32 for subjects with a Pb-B of 2.41 to 3.84 $\mu\text{mol/L}$ and a Ht% mean

of 41 for controls with a Pb-B of 0.48 to 1.20 $\mu\text{mol/L}$. Our results would also have been skewed toward short stature if expressed as a mean, and the fact obscured that the majority of our patients were in or above the 50th Ht%. For example, the mean Ht% of patients with a Pb-B of 7.23 to 9.60 $\mu\text{mol/L}$ was 45, yet 61% were in the 50th to 95th Ht%.

Schwartz et al⁸ deduced from their analysis of National Health and Nutrition Examination Survey⁹ data that stature is inversely correlated to Pb-B, and that Pb-Bs of 0.24 to 1.68 $\mu\text{mol/L}$ are statistically significant predictors of children's height ($P < .0001$), weight

($P < .001$), and chest circumference ($P < .026$). Since the National Health and Nutrition Examination Survey estimated that only 4% of children have Pb-Bs above 1.44 $\mu\text{mol/L}$, can chance lead tests made between 6 months and 5 years of age govern the order of height of 96% of the population? Their analysis refutes the accepted genetic relationship between parents' and children's heights.^{10,11}

CONCLUSION

Our patients not only experienced severe lead poisoning but twice ran the low level gamut, as they ascended from, then descended to, the normal range for

Pb-B. Thus they are uniquely qualified for an inquiry into sequelae of all Pb-Bs. With respect to Ht% and Wt%, about 70% placed in the 50th to 95th percentiles, from childhood through adoles-

cence, skewing the normal distribution of Ht% and Wt% to the right. Furthermore, during years of observation, they maintained a consistent similarity to their unaffected sibs in those param-

ters. Blood lead at any concentration did not seem to affect growth or alter the genetic predisposition for eventual adult height.

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In Other AMA Journals

JAMA

The Inexact Use of Fisher's Exact Test in Six Major Medical Journals

W. P. McKinney; M. J. Young; A. Hartz; M. B. F. Lee (*JAMA*. 1989;143:3430-3433)

The Use of Purified Clotting Factor Concentrates in Hemophilia

G. F. Pierce; J. L. Lusher; A. P. Brownstien; J. C. Goldsmith; C. M. Kessler (*JAMA*. 1989;143:3434-3438)

Nonaggressive Obstetric Management

F. A. Chervenak, L. B. McCullough (*JAMA*. 1989;143:3439-3440)

Manganese Absorption From Human Milk, Cow's Milk, and Infant Formulas in Humans

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• Manganese absorption from human milk, cow's milk, and infant formulas was studied in humans by using extrinsic labeling of the diets with manganese 54 or manganese 52 and whole-body retention measurements. The fractional manganese absorption from human milk ($8.2\% \pm 2.9\%$) was significantly different when compared with cow's milk ($2.4\% \pm 1.7\%$), soy formula ($0.7\% \pm 0.2\%$), and whey-preponderant cow's milk formula with 12 mg/L of iron ($1.7\% \pm 1.0\%$) and without iron fortification (2 mg/L of iron) ($3.1\% \pm 2.8\%$), while no significant difference was observed between a whey-preponderant cow's milk formula with 7 mg/L of iron ($5.9\% \pm 4.8\%$) and human milk. The total amount of absorbed manganese was significantly higher from the non-iron-fortified cow's milk formula (2 mg/L of iron) as compared with human milk, while no significant differences were observed for the other milks and formulas. (AJDC. 1989;143:823-827)

There has been little focus on the role of manganese in infant nutrition, and manganese nutrition in the neonatal period is poorly understood, partly because of the lack of information on manganese content in infant foods and its bioavailability. In experimental animals, manganese deficiency has been shown to have severe effects on prenatal and postnatal development.¹ No cases of documented manganese deficiency have yet been reported in human infants, although concern about the risk for devel-

oping manganese deficiency has been discussed, especially for premature and low-birth-weight infants.^{2,3} This absence of cases, however, may also be from the lack of diagnostic tests for manganese deficiency. In contrast to iron, zinc, and copper, manganese stores are not thought to be accrued prenatally^{4,5}; thus, the infant may be particularly susceptible to manganese deficiency. Full-term infants have been described to be in negative manganese balance,² and very-low-birth-weight infants were shown to have an impaired manganese status, as assessed by manganese concentration in the hair.³ Some convulsive disorders have been proposed to be related to manganese deficiency.^{6,8} The low manganese level in blood observed in some young children has been postulated to be caused by an insufficient supply of manganese in utero or after birth.⁶

The toxic side effects of manganese may also be a problem early in life, since the manganese concentration of some infant formulas is high, in some cases exceeding the concentration in human milk by a factor of 200.^{9,10} This high concentration of manganese may be potentially deleterious to infants, since manganese homeostasis is mainly regulated through excretion via bile,¹¹ and biliary excretion is not established early in life.¹² In the adult human, it is well known that manganese toxicosis can have severe effects, particularly with regard to the central nervous system. Thus, a high supply of manganese during the neonatal period may be as detrimental to the infant as a deficiency.

Information on the bioavailability of manganese from infant diets is needed to establish a range for "safe and adequate daily dietary intake" for infants. Data from animal studies have shown that manganese absorption can be influenced by the level of iron¹³ and calcium¹⁴

as well as by other dietary factors, such as phytic acid intake.¹⁵ The content of these dietary components varies in milks and formulas, and it has been reported that some of these factors can affect trace element absorption, eg, zinc absorption from infant diets.¹⁶ We have recently developed a sensitive method to study manganese absorption in humans.¹⁷ The method involves feeding an extrinsically labeled test meal to an adult human and subsequently monitoring the whole-body retention of the administered radioisotope in a very sensitive whole-body counter. The aim of this study was to compare manganese absorption from human milk with cow's milk and infant formulas (based on cow's milk or soy), as well as to study the effect of iron fortification of formulas.

SUBJECTS AND METHODS

Subjects

Thirty-nine subjects, 12 men and 27 women, volunteered for the study. They were all healthy, none of the women were pregnant, and none of them had a history of gastrointestinal dysfunction. The mean age was 28 years (range, 21 to 45 years). None of the subjects was consuming vitamin or mineral supplements or any other medication during the study. Subjects were given written and oral information about the aims and procedures of the study, and informed consent was obtained from all participating subjects. The project was approved by the Ethical Committee and by the Isotope Committee of Sahlgrenska Hospital, University of Gothenburg, Göteborg, Sweden, and by the Human Subjects Committee at the University of California, Davis.

Diets

The following milks and formulas were used: (1) pooled and pasteurized human milk obtained from the milk bank at the Östra Hospital, Göteborg; (2) pasteurized and homogenized cow's milk (with 3% fat, purchased from a local vendor); (3) powdered,

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whey-preponderant (60/40) cow's milk formula (Baby Semp 1, Semper AB, Stockholm, Sweden); (4) whey-preponderant (60/40) cow's milk formula (Enfamil, Mead Johnson, Evansville, Ind), either iron fortified (12 mg/L of iron, diet a) or the same formula without iron fortification (2 mg/L of iron, diet b); and (5) soy formula (Prosoabee, Mead Johnson). Milks and formulas were pooled and kept frozen in 450-g serving portions until used. Fifty-five grams of the powder (diet 3) was dissolved in deionized water (395 g); all other formulas were in liquid form. Milks and formulas were extrinsically labeled with 0.1 to 0.2 millibecquerel of manganese 54 or 0.3 mBq of manganese 52 before being served.

Paired observations were used to compare the manganese absorption from human milk with cow's milk (subjects 1 through 8) and to evaluate the influence of iron fortification (diet 4, subjects 23 through 30) as well as to compare the manganese absorption from the soy formula with whey-preponderant cow's milk formula with a high iron content (diet 4a, subjects 31 through 39). The whey-preponderant cow's milk formula in diet 3 was given as one single administration to 14 subjects (subjects 9 through 22).

Radioisotopes

The ^{54}Mn was purchased commercially for use in this study. The ^{52}Mn was produced for this study in the cyclotron at the Department of Physics, University of Oslo, Norway.¹⁸ Individual portions of the radioisotope stock solutions were diluted in deionized distilled water to a volume of 2 mL in standardized plastic capsules. The portions were measured in an activity calibrator and then added to the milk or formula before it was served. The empty vials were measured separately in the whole-body counter after the subjects had consumed the fluid.

Experimental Design

The subjects arrived in the morning after 12 hours of fasting. Measurements of height and weight were registered, and each subject's background radioactivity was measured in the whole-body counter. Blood samples were drawn in the fasting state for determination of the whole-blood manganese and iron status. The extrinsically labeled test meal was served, and a 100% value of administered activity was obtained by measurement in the whole-body counter immediately after intake. No other food or fluid was allowed during the next 3 hours. The subjects maintained their normal food intake during the study. The two test meals were served on 2 consecutive days with ^{54}Mn and ^{52}Mn as a label, or with a time lapse of approximately 2 months when ^{54}Mn was administered twice. Whole-body retention measurements were

performed two to three times weekly during approximately 30 days after initiating the study.

The whole-body counter laboratory at the Radiation Physics Department at the University of Gothenburg is equipped with a double-chamber iron room with 150-mm-thick walls containing two different detector systems for whole-body measurements.¹⁹ Detector system 1, which was used in this study, consists of two 130 × 100-mm sodium iodide (TI) detectors (Bicron Corp, Newbury, Ohio) mounted on opposite sides of a patient couch and attached to a motor-driven *x-y* scanning system. The most important property of these detectors is their spectral resolution that enables studies of more than one isotope simultaneously in the body; in this case, we were able to measure ^{52}Mn in the presence of ^{54}Mn when the two radioisotopes were administered on consecutive days.¹⁸ Manganese absorption was calculated by extrapolation to day 0 from whole-body retention measurements during days 10 through 30.¹⁷ The resulting radiation exposure of the subjects was evaluated using the model of the International Commission on Radiological Protection,^{20,21} which gives the exposure of the whole body (effective dose equivalent) after ingestion of a certain activity. In this study, the radiation exposure was 0.07 to 0.6 mSv to each subject.

Analysis

Indexes of iron status were determined by routine laboratory methods. Whole-blood manganese was analyzed by electrothermal atomic absorption (using a Perkin Elmer Zeeman/3030 instrument equipped with graphite furnace HGA 600; Perkin Elmer, Überlingen, West Germany). Magnesium nitrate was used as a matrix modifier.²² Aliquots of milks and formulas were freeze-dried and homogenized before analysis. The manganese content in the diets was analyzed by electrothermal atomic absorption. Before analysis, the food items were wet ashed in an autoclave (Perkin Elmer Autoclave-3), 1 g of freeze-dried sample was added to 6 mL of 7 mol/L of nitric acid and heated to 160°C during 1 hour. After wet ashing, the samples were made up to 25 mL with deionized distilled water. The content of minerals (iron, calcium, and magnesium) was determined by atomic absorption spectrophotometry (Perkin Elmer Model 360). An analysis of iron content was done after dry ashing (450°C), while concentrations of calcium and magnesium were determined after wet ashing (290°C to 300°C) in sulfuric acid and hydrogen peroxide and after the addition of lanthanum oxide. The same digest was used to determine phosphorus concentrations by the Fiske-Subbarow method.²³ Nitrogen analysis was performed by a micro-Kjeldahl tech-

nique (Technicon Autoanalyzer, Ardsley, NY). Phytic acid content in the soy formula was determined as described by Davies and Reid.²⁴

Statistics

For statistical evaluation of absorption data, Student's *t* test for paired samples was used for comparison of diets 1 and 2, 4a and 4b, and 5 and 4a. Analysis of variance and Duncan's New Multiple-Range Test was used for tests of statistical significance when other comparisons were made (Mulreg 800; Idatron, Linköping, Sweden).

RESULTS

The mean whole-blood manganese concentration of the participating subjects was 0.22 $\mu\text{mol/L}$ (range, 0.13 to 0.37 $\mu\text{mol/L}$). Analyzed laboratory values were as follows: hemoglobin, 122 to 150 g/L for women and 139 to 166 g/L for men; serum iron, 10 to 30 $\mu\text{mol/L}$ for women and 13 to 40 $\mu\text{mol/L}$ for men; and total iron-binding capacity, 48 to 76 $\mu\text{mol/L}$ for both women and men. All values for whole-blood manganese and iron status indexes were within the normal range for our laboratory. Concentrations of nitrogen, iron, calcium, phosphorus, and magnesium in the milks and formulas studied are given in Table 1. The concentration of phytic acid in the soy formula was 460 $\mu\text{mol/L}$. The content of manganese and iron in the diets and manganese absorption from the diets are shown in Table 2.

Fractional manganese absorption from human milk was significantly higher than the absorption of manganese from cow's milk, whey-preponderant cow's milk formula (with or without iron fortification, diets 4a and 4b), and soy formula. No significant difference was observed, however, between human milk and the whey-preponderant cow's milk formula with 7 mg/L of iron, diet 3. The manganese absorption from this formula (diet 3) was significantly different from that of the other test meals. No significant difference in manganese absorption was observed after the administration of the two formulas differing only in iron content (diets 4a and 4b) to the same group of subjects. The administration of soy formula was found to result in a significantly lower fractional manganese absorption compared with the iron-fortified cow's milk formula (diet 4a) when results from the paired

Diet	Nitrogen, g/L	Iron, mg/L	Calcium, mg/L	Phosphorus, mg/L	Magnesium, mg/L
1. Human milk	2.4	0.7	294	200	32
2. Cow's milk	5.1	0.2	1033	737	65
3. Cow's milk formula (Baby Semp 1)	2.2	7	392	303	54
4a. Cow's milk formula (Enfamil), iron fortified	2.4	12	427	303	76
4b. Cow's milk formula (Enfamil), non-iron fortified	2.3	2	410	303	76
5. Soy formula (Prosobee)	3.1	12	454	475	70

Diet	Subjects	Manganese, μ g	Iron, mg	Manganese Absorption*	
				%	μ g
1. Human milk	1-8	7.2	0.27	8.2 \pm 2.9 ^a	0.59 \pm 0.21 ^a
2. Cow's milk	1-8	44	0.13	2.4 \pm 1.7 ^b	1.06 \pm 0.75 ^{a,b}
3. Cow's milk formula (Baby Semp 1)	9-22	23	3.0	5.9 \pm 4.8 ^a	1.36 \pm 1.10 ^{a,b}
4a. Cow's milk formula (Enfamil), iron fortified	23-30 and 31-39	59	5.6	1.7 \pm 1.0 ^b	1.00 \pm 0.59 ^{a,b}
4b. Cow's milk formula (Enfamil), non-iron fortified	23-30	59	1.0	3.1 \pm 2.8 ^b	1.83 \pm 1.65 ^b
5. Soy formula (Prosobee)	31-39	132	7.2	0.7 \pm 0.2 ^b	0.92 \pm 0.26 ^{a,b}

*Values are given as means \pm SDs. Values with different superscript letters within each column were significantly different ($P < .05$) (using analysis of variance and Duncan's New Multiple-Range Test).

observations were evaluated ($P < .02$). Due to the differences in manganese content, the total amount of absorbed manganese was significantly higher from the whey-preponderant cow's milk formula without iron fortification (diet 4b) as compared with human milk, while no significant differences were observed when the total amount of absorbed manganese was calculated for the other milks and formulas studied.

COMMENT

There is a pronounced effect of age on the percentage of manganese retained from a meal in young rats.^{26,28} A higher capacity for manganese absorption and retention in young animals compared with older animals may be a consequence of the scarcity of this essential

trace metal in the diet.²⁷ Raghib et al²⁶ proposed that the observed effect of age on manganese absorption might be caused by the degree of passive transport and that the lower manganese absorption by older rats might be caused by intestinal maturation rather than by the nutritional need for manganese. In our study, manganese absorption from infant diets was studied in adults. Whether the differences found between diets would be more pronounced when studied in infants is not known, although this seems to be the case for zinc, when studied in monkeys.²⁸

Manganese absorption was estimated in adult humans by using a radioisotope technique in this study. Highly reproducible figures for manganese absorption within the same individual have

been found using this technique.¹⁷ Inter-individual variation in manganese absorption was shown, however, to be substantial, indicating that the best way to identify factors influencing manganese absorption is by paired observations, with subjects acting as their own controls. Because of practical reasons, diet 3 was given as one single test meal, while the other diets were served at two occasions, eg, human vs cow's milk, to the same subject to obtain paired observations. The administration of ⁵⁵Mn and ⁵⁴Mn was done on consecutive days when possible. However, ⁵⁵Mn is not available commercially but was produced for this study. Because of the short half-life (5.7 days) and the tedious procedure of production, the isotope was not available at all times during the study. Consequently, ⁵⁴Mn was used as an extrinsic label for both diets.

The validity of the extrinsic labeling of the meals has been reported earlier.^{18,29} Equal distribution of native manganese and the added radioisotope within individual fractions of human milk, cow's milk, and infant formulas were demonstrated and can be regarded as an indirect validation of the extrinsic labeling technique for these particular diets.²⁹ The method has also been directly validated using simultaneous measurements of ⁵⁴Mn and ⁵²Mn added intrinsically and extrinsically to chicken liver.¹⁸

Human milk and formulas have previously been evaluated with regard to manganese absorption in animal studies and in a few studies of human infants. A high bioavailability of manganese during the suckling period in rats has been reported for infant diets.²⁶ The mean relative retention of manganese, measured by a chemical balance technique in infants, was 43% for human milk and 20% when cow's milk formula was fed.³⁰ Our results demonstrated high bioavailability of manganese from human milk. This is consistent with earlier studies in which high bioavailability of trace minerals in human milk has been reported for zinc,¹⁵ iron,³¹ and copper.³² The reasons for the difference in manganese absorption from human milk as compared with cow's milk are not yet known. It is not likely to be caused by the difference in manganese concentration, however, as manganese absorption from a vitamin and mineral supple-

ment containing 2.5 mg of manganese sulfate was found to be $9\% \pm 3\%$ when the supplement was taken in a fasting state by six healthy subjects.³³ A possible explanation of the differences in manganese absorption between human milk and cow's milk is that manganese in human milk, but not in cow's milk, is bound to lactoferrin.³⁹ Lactoferrin has been shown to bind to a specific receptor in the small intestine,³⁴ and it has recently been shown that lactoferrin efficiently delivers not only iron but also manganese.³⁵ Lactoferrin may therefore provide a mechanism for manganese absorption from human milk as well as for iron absorption. Furthermore, cow's milk contains a considerably higher amount of calcium as compared with human milk, which may have influenced the manganese absorption. The adverse effect of calcium on manganese absorption has been reported.¹⁴

The interaction between iron and manganese has been demonstrated in several investigations.^{13,36-39} In this study, we found that the iron fortification of the cow's milk formula (diet 4a) led to a lower mean fractional manganese absorption as compared with the identical formula without iron supplementation (diet 4b), although the difference was not statistically significant. Administration of the cow's milk formula with 7 mg/L of iron (diet 3) was shown to result in a significantly higher manganese absorption as compared with the cow's milk formula containing 12 mg/L of iron (diet 4a) as well as compared with the non-iron-fortified formula (diet 4b). The differences observed in manganese absorption from whey-preponderant cow's milk formulas can thus not be explained by the different iron content. A possible factor influencing manganese absorption is, however, the protein composition. The cow's milk formulas (diets 3, 4a, and 4b) were all whey-preponderant (60/40). However, there are significant differences in the nitrogen and nonprotein nitrogen composition of formulas from different manufacturers. These differences are from the use of heat treatment during processing and depend on the source of whey used for the whey adjustment.⁴⁰

The low fractional manganese absorption from soy formula demonstrated in this study is consistent with

results from animal studies.²⁵ The low bioavailability of zinc in soy formula has been demonstrated in adult humans with the use of a radioisotope technique.¹⁶ Soy formula contains a considerable amount of phytic acid and proteins with different characteristics as compared with the other infant diets studied,⁴⁰ which may, at least in part, explain the low fractional manganese absorption from soy formula.

Since most formulas contain a considerably higher manganese content than what is found in human milk, manganese deficiency may be less of a concern than the toxic side effects of manganese when formulas are fed. When the total amount of absorbed manganese was calculated, the whey-preponderant cow's milk formula with low iron content (diet 4b) provided three times as much manganese as human milk ($P < .05$). This high amount of absorbed manganese might be detrimental to the child since excretion of manganese is low early in life.^{11,12} Thus, the body burden of manganese might be significantly increased in formula-fed infants as compared with breast-fed infants.

The optimum amount of manganese as well as the ratios between the content of different trace elements in infant diets need to be determined. Studies of manganese absorption in infants as well as further studies to identify factors affecting manganese absorption are needed before "a safe and adequate" range for manganese intake can be established.

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Book Review

Otitis Media in Infants and Children, by C. D. Bluestone and J. O. Klein, 288 pp, with illus, \$39.95, Philadelphia, Pa, WB Saunders Co, 1987.

This useful book has 10 chapters, the first 6 dealing with basic sciences and the last 4 addressing clinical disease and management. The authors are well qualified, having written more about this subject than any of their contemporaries. All their publications have reflected well-constructed, controlled studies.

Caveats for initial evaluation of children with otitis media are presented, coupled with a brief differential diagnosis of other conditions that cause conductive hearing loss: traumatic or erosive ossicular chain disruption and atelectasis of the tympanic membrane associated with ossicular discontinuity or an acquired cholesteatoma. There is an excellent section on normal eustachian tube function and dysfunction due to maldevelopment of the cranial base or intrinsic mechanical obstruction by polyps or cholesteatoma.

Knowledge of the epidemiology of middle-ear disease in children is a recent development. Longitudinal studies of American Indian and Alaskan children are presented. Otitis media unrecognized by parents, because it was asymptomatic, can be diagnosed using immittance studies and audiograms and by pneumatic otoscopy. Sex, race, socioeconomic factors, congregating children in child-care facilities, season of the year, genetic factors, breast-feed-

ing, and effects of altered host defenses or underlying disease singly or as a result of multiple factors may contribute to the size and complexity of the problem. Relevant microbiologic and immunologic studies are reviewed in a detailed, well-classified format. The signs and symptoms are described, along with a chart showing tympanogram types and variants related to clinical findings, which will be useful to the general physician and pediatrician. The chapter on diagnosis is quite complete, with discussions of otoscopy, tympanograms, acoustic reflexometry, and auditory brain responses. Various techniques of obtaining hearing thresholds on children are well illustrated. Sections on high-risk populations, the deaf, and methods of collecting specimens are included. Clinical eustachian tube tests are also described clearly.

Options for managing various stages of otitis media represent most of the philosophies in this country. An algorithm is provided. Another table provides a daily dosage schedule for useful antimicrobial agents in otitis media and likely would be a valuable quick reference, complete with dosages per unit weight of the child.

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Risk Factors for Infant Botulism in the United States

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• To define risk factors for infant botulism, we performed a 2-year prospective case-control study of 68 laboratory-confirmed cases in infants living in the United States, outside of California. For each case patient, two control subjects were matched by date and hospital of birth or county birth records. By univariate analysis, breast-feeding (odds ratio=2.9) and consumption of honey (odds ratio=9.8) were associated with disease, but only 11 case patients (16%) had eaten honey. Decreased frequency of bowel movement (less than one per day for at least 2 months) was also associated with disease in infants 2 months of age and older (odds ratio=5.2). Risk factors changed with the age of the patient at disease onset when analyzed by multivariate logistic regression methods. For infants less than 2 months old, living in a rural area or on a farm was the only significant risk factor (odds ratio=6.4). For infants 2 months of age and older, breast-feeding (odds ratio=3.8), less than one bowel movement per day for at least 2 months (odds ratio=2.9), and ingestion of corn syrup (odds ratio=5.2) were associated with disease. The severity of the disease was similar for breast- and bottle-fed infants. Clearly defined food exposures account for a minority of infant botulism cases. Preexisting host factors, such as intestinal flora and frequency of bowel movements, may be the most important risk factors for development of disease.

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Over 600 cases of infant botulism have been reported in the United States¹ since the first description of this disease in 1976,² making it the most common form of botulism identified in this country. Epidemiologic studies have identified consumption of honey and breast-feeding as risk factors for disease.^{3,4} Spores of *Clostridium botulinum* of the same toxin type causing disease have been isolated from honey fed to infants before onset of illness.^{3,6} Although 27% to 29% of patients described in two large

early studies received honey,^{3,6} this exposure is now identified for about 15% of cases reported to the Centers for Disease Control (CDC), Atlanta, Ga, through a nationwide surveillance system for infant botulism (unpublished data, 1935). No other potential food source in infants for *C botulinum* spores has been epidemiologically implicated. However, spores have occasionally been isolated from corn syrup.⁷ Epidemiologic and microbiologic evidence implicating commercial food products would support interventions aimed at better consumer education.

The role of breast-feeding remains controversial. From 66% to 100% of patients with infant botulism described in previous studies have been breast-fed.^{4,6,9} These infants were predominantly white, and their mothers tended to be older and have more years of education than the general population,⁶ factors associated with a greater tendency to breast-feed.¹⁰ These studies have not determined if breast-feeding contributes to infant botulism or if breast-feeding is simply a confounding factor that, like some as yet undetermined causal factor, is associated with socioeconomic status.

Breast-fed infants may have better access to physicians more likely to make the diagnosis. It has been proposed that breast-fed infants with infant botulism are identified because they have milder disease with later onset, while non-breast-fed infants present earlier with a clinical picture identical to sudden infant death syndrome.⁸ We performed a case-control study to better define the role of breast-feeding as a risk factor for disease and to identify other foods and host and environmental factors that may contribute to acquisition of infant botulism.

METHODS

All laboratory-confirmed cases of infant botulism outside of California reported to CDC with onset of disease from April 1, 1985, to March 31, 1987, were eligible for inclusion in the study. Most state laboratories do not test for *C botulinum* or its toxin and send stool specimens from suspected cases of bot-

ulism to CDC for analysis. State laboratories that process specimens from suspected cases of botulism report all laboratory-confirmed illness to CDC.

Following notification, we interviewed by telephone the patient's physician regarding the illness and hospitalization and obtained permission to interview the case patient's family. Each case patient was matched with two control subjects by identifying the next four infants who were born after the case patient at the hospital of birth. Information was obtained on the first two identified infants who were alive and living at home and whose physician and parents agreed to participate. For six case patients, the names of potential matching control subjects were obtained from records of the case patient's county of current residence for births on the same day. Two were born at home, two had moved to another state at least 1 month before onset of illness, and the hospital of birth refused to identify control subjects for two of the infants.

Case patients' and control subjects' families were interviewed by telephone using a standardized questionnaire. Case patients' families were asked about signs associated with infant botulism and the date each sign was first noticed. Since the onset of infant botulism can be insidious, onset of illness was defined as the date the patient was first seen by a medical person for illness subsequently identified as infant botulism.

Information was obtained from the families of case patients and control subjects about sources of medical care for the infant, previous medical problems, immunizations, the mother's pregnancy, the infant's usual bowel movement (BM) pattern by month of life (at least one BM per day; less than one BM per day, but at least one BM per 3 days; or less than one BM per 3 days), occupation, and educational levels of both parents, and usual activities around the home. Information about type and quantity of all food exposures, supplemental vitamins, pacifier use, location of residence (defined by the parent as city, suburban, rural, or on a farm), and environmental events was obtained for the 1-month period before onset of illness.

Parents were asked to quantify breast-milk consumption as a percentage of all milk or formula fed during the month. Specific questions were asked about events that occurred within 300 ft of the home, including construction (new home or other building), excavation (sewers or new foundations), new road construction, plowing of fields, and environmental changes (remodeling of home or

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major landscaping). If an infant spent at least 20 hours per week at a location other than his home during the 1-month period, similar information was obtained about that location from a source identified by the parent.

A socioeconomic status score was determined for the family (parent's highest score) using the index of Stevens and Featherman.¹¹ Exposures in case patients and control subjects were compared using the Pike and Morrow extension of the Mantel-Haenszel χ^2 test.¹² Where indicated, the χ^2 test for linear trend and multivariate logistic regression analysis¹³ were used.

RESULTS

Sixty-eight (99%) of 69 laboratory-confirmed cases of infant botulism (33 type A and 35 type B) that were reported to CDC with onset of disease April 1, 1985, to March 31, 1987, were included in the study. One patient (type A) was excluded because control subjects matched from county records could not be contacted. The median age of the 68 case patients at "onset of illness" was 2.0 months (range, 0.2 to 11.7 months). Fifty-three percent were female. Sixty-six case patients (97%) were hospitalized for a median of 27 days (range, 1 to 152 days) and 28 (42%) required ventilator support for a median of 19 days (range, 4 to 80 days).

The most common first symptoms observed by parents were poor feeding (52%), less than one BM per 3 days (47%), and altered cry (25%). Forty-seven (69%) had less than one BM per 3 days for a median of 4 days (range, 0 to 117 days) when first seen with symptoms of botulism by a medical person. One patient had a respiratory arrest after botulism was diagnosed, suffered severe brain damage, and died 6 months later.

Two control families were interviewed for each of 67 case patients. Only one control family was interviewed for 1 of the case patients. Information on case patients and control subjects for some of the variables examined is presented in Table 1. Among food items, significant differences between groups were detected only for exposure to breast milk and honey during the month before onset of illness in the case patient. Corn syrup was used by 29% of the case patients and 19% of the control subjects. Overall, control subjects had foods other than breast milk introduced earlier

Table 1.—Comparison of Case Patients and Control Subjects for Selected Features

Characteristics	No. (%)		Odds Ratio (95% Confidence Interval)	P Value
	Case Patients (n=68)	Control Subjects (n=135)		
Sex, F	36 (53)	66 (49)	1.2 (0.7, 2.1)	.562
Normal birth	44 (65)	100 (74)	1.6 (0.8, 3.0)	.168
Mean maternal age, y	27.6	27.5	1.0 (0.9, 1.0)	.803
Maternal education				
≤12 y	37 (54)	68 (51)	0.9 (0.5, 1.7)	.749
≥16 y	13 (19)	22 (17)	1.3 (0.5, 3.0)	.569
No. of siblings				
None	28 (41)	47 (35)	0.7 (0.4, 1.4)	.352
Median	1	1	...	
Mean family occupational status index*	43.4	45.5	1 (1, 1.0)	.430
Breast-fed				
<50%	50 (74)	64 (47)	2.8 (1.5, 5.4)	.001
50%–<100%	28 (41)	31 (23)	2.6 (1.3, 5.1)	.011
100%	15 (22)	25 (19)	1.2 (0.6, 2.5)	.582
Corn syrup	20 (29)	25 (19)	1.8 (0.9, 3.6)	.093
Honey	11 (16)	3 (2)	9.8 (2.2, 44.7)	.004
Iron (formula or vitamins)	42 (62)	76 (56)	1.3 (0.6, 2.7)	.447
Pacifier use (any)	47 (69)	79 (59)	1.7 (0.9, 3.3)	.136
Decreased bowel movements for ≥2 mo†	23 (66)	13 (19)	5.2 (1.9, 14.3)	.003
Residence				
City/town‡	33 (49)	73 (54)	1.3 (0.7, 2.4)	.465
Suburban	19 (28)	43 (32)	0.8 (0.4, 1.7)	.529
Rural/farm	17 (25)	19 (14)	2.3 (1, 5.4)	.052
Construction, excavation, or plowing <300 ft from home	28 (41)	53 (40)	1.1 (0.6, 1.9)	.803

*Based on the Stevens and Featherman¹¹ index.

†This category includes a total of 35 case patients and 70 control subjects at least 2 months old.

‡One case patient moved from city to suburb during the month before illness onset and is included in both locations.

than case patients. However, no difference was found when infants receiving formula at birth were excluded from the analysis.

Decreased frequency of BM was associated with illness. Thirty-seven (64%) of 58 case patients at least 1 month old had a usual monthly pattern before onset of illness of one BM per day compared with 17 (15%) of 115 control infants ($P<.001$; odds ratio=13.8; 95% confidence interval=4.9, 39.1). Forty-seven percent of the case patients and 14% of the control subjects had less than one BM per day, but had at least one BM every 3 days during this period ($P<.001$; odds ratio=6.7; 95% confidence interval=2.7, 16.4). Since "constipation" is a prominent symptom of infant botulism reported in the litera-

ture and its presence for more than a few days could affect the reported usual monthly pattern, we determined the number of infants with less than one BM per day for 2 months before onset of illness (Table 1). The association with less than one BM per day remained significant.

Case patients were more likely than control subjects to have lived in a rural area or on a farm. Differences between case patients and control subjects were not detected for frequency of dusting or vacuuming at home, type of home heating and cooling systems, number and location of house plants, or frequency of gardening by family members. Eighteen percent of the case patients and 15% of the control subjects spent at least 20 hours per week away from home

during the month before the case patient's illness. No significant differences were detected when these exposures were analyzed.

To determine whether the increased use of corn syrup by case patients was due to their greater likelihood of receiving corn syrup for treatment of decreased frequency of BM, corn syrup use was stratified by frequency of BM during the 2-month period before onset of illness in the case patient. Only infants 2 months of age or older were included in the analysis. Among infants with at least one BM per day for the 2-month period, 44% of 9 case patients and 13% of 47 control subjects had ingested corn syrup. Among those with less than one BM per day, 29% of 17 case patients and 18% of 11 control subjects had ingested corn syrup. Matched analysis could not be done because of an insufficient number of case patient and control subject pairs and triplets.

Analysis of infants by multivariate linear logistic regression analysis using risk factors identified as significant ($P \leq .05$) or of borderline significance ($P < .1$) in univariate analyses is shown in Table 2. No significant interactions were detected among the variables included in these analyses. Breast-feeding and honey ingestion during the month before onset of illness were significant risk factors when rural or farm residence and consumption of corn syrup were controlled.

Separate logistic models were developed for infants less than 2 months old ($n = 98$) and 2 months of age and older ($n = 105$) so that BM pattern (less than one BM per day) during the 2 months before onset of illness could be analyzed. Honey was not included in these models because case patients and control subjects exposed to honey were divided between the less than 2-month-old group and the 2-month and older group; the number of infants in each group was too small. Only rural or farm residence was associated with disease in the younger than 2-month-old group; this variable was not a risk factor for those 2 months of age or older. Breast-feeding, decreased BM frequency, and corn syrup were risk factors for the 2-month and older group (Table 2), although decreased BM frequency had only borderline significance ($P = .072$).

Table 2.—Multivariate Logistic Regression Analysis of Selected Risk Factors

Model	No. of Case Patients	No. of Control Subjects	Odds Ratio	95% Confidence Interval	P Value
Model 1 (all infants)					
Honey	16	2	8.3	1.7, 39.3	.007
Corn syrup	29	19	2.0	0.9, 4.6	.097
Breast-fed	74	47	3.3	1.6, 6.6	.001
Rural/farm*	25	14	1.9	0.8, 4.8	.161
Model 2 (98 infants <2 mo old)					
Corn syrup	24	25	1.1	0.4, 3	.888
Breast-fed	67	54	1.4	0.5, 3.9	.549
Rural/farm	40	15	6.4	1.4, 30.6	.018
Model 3 (105 infants ≥2 mo old)					
Corn syrup	34	13	5.2	1.2, 22.2	.024
Breast-fed	80	41	3.8	1.4, 10.5	.011
Rural/farm	11	13	1.1	0.3, 4.6	.936
Decreased bowel movements†	66	19	2.9	0.9, 9.5	.072

*The infants lived in a rural area or on a farm during the month before onset of illness.

†The infants had less than one bowel movement per day for at least 2 months before onset of illness.

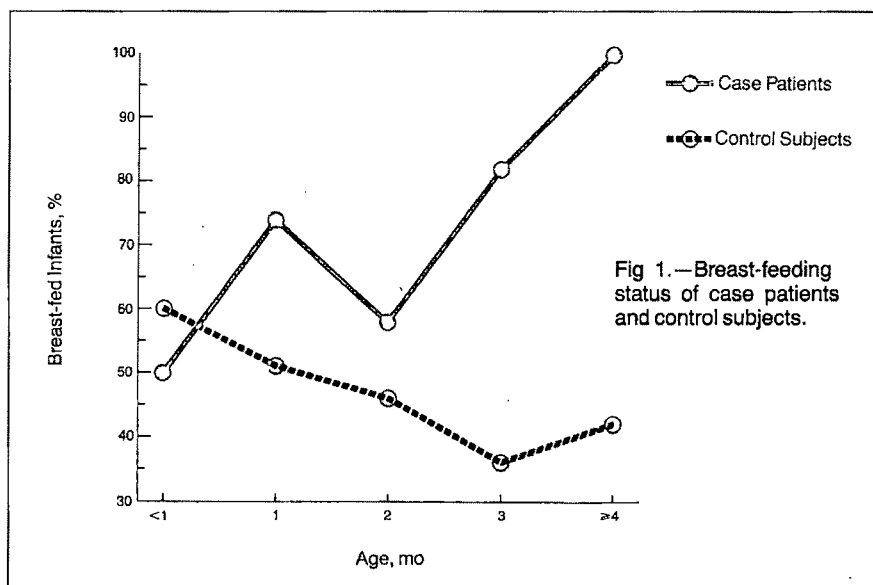


Fig 1.—Breast-feeding status of case patients and control subjects.

To evaluate whether confounding was present in the multivariate logistic model for infants 2 months of age and older, we included corn syrup ingestion, breast-feeding, and rural/farm residence individually with decreased BM frequency in separate logistic models. Decreased BM frequency was a significant risk factor in each model with odds ratios that varied between 3.8 and 5.3. The odds ratio for decreased BM fre-

quency was always greater than the odds ratio for the other variable. This suggested to us that the change in level of significance for decreased BM frequency in the model with all four variables was due to inadequate power with a small number of case patients and control subjects.

The percentage of case patients and control subjects breast-fed by age at disease onset is shown in Fig 1. There

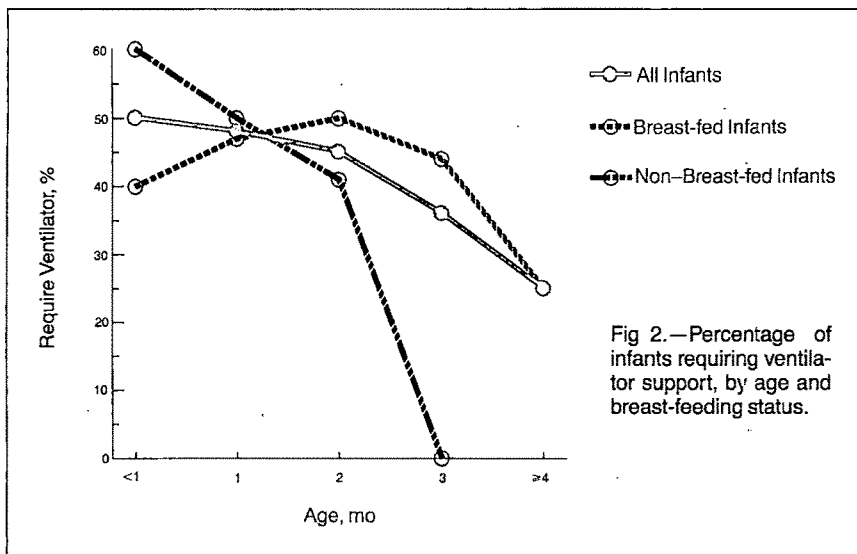


Fig 2.—Percentage of infants requiring ventilator support, by age and breast-feeding status.

was a trend toward increased breast-feeding with increasing age among case patients ($P = .014$, χ^2 for linear trend). However, the difference between case patients and control subjects by matched analysis was not significant until 3 months of age ($P = .05$; odds ratio = 4.9; 95% confidence interval = 1.0, 24). To examine the effect of breast-feeding on severity of disease, we looked at the percentage of infants requiring ventilator assistance by age and breast-feeding status (Fig 2). There was a tendency toward greater need for ventilator assistance with younger age, but this was not significant ($P = .122$, χ^2 for linear trend). No marked difference was seen between breast-fed and non-breast-fed infants.

COMMENT

The results of this study demonstrate that decreased frequency of BM 1 and 2 months before onset of illness is associated with acquiring infant botulism. Decreased BM frequency has not been recognized previously as a risk factor, although infants may have several weeks of constipation before the appearance of other symptoms.¹⁴ It has been difficult to determine whether constipation is a risk factor for, or a result of, the disease because the incubation period for infant botulism is unknown. However, epidemiologic and clinical information suggest that the incubation period is less than 1 month. In this study, 10 infants (15%) were younger than 30 days of age when first seen by a

medical person for their illness, and 1 infant was only 6 days old. The 47 infants who had at least one BM every 3 days before they were seen by a medical person had had this BM pattern for a median of only 4 days before the visit. It is unlikely that the 23 case patients (66%) at least 2 months old with decreased BM frequency all had incubation periods of 2 months or longer.

Decreased BM frequency may be a sign of decreased intestinal motility, which could give ingested *C botulinum* spores increased opportunity for germination and toxin production. In adults, decreased motility can be reflected in decreased stool volume,¹⁵ and may contribute to the bacterial overgrowth syndrome.¹⁶ Decreased motility may also permit retrograde movement of *C botulinum* or its toxin from the colon into the ileum. In adult germ-free mice, removal of the cecum prevents colonization by *C botulinum* and development of botulism after challenge with spores.¹⁷ However, it is thought that most toxin is absorbed from the small intestine, because morbidity in mice following challenge with spores is better correlated with the amount of toxin present in the small intestine than with the amount in the colon,¹⁸ and toxin injected into the colon of rhesus monkeys is poorly absorbed.¹⁹

Consumption of honey continues to be associated with infant botulism. Unlike the earlier report identifying an association only between honey ingestion and disease with *C botulinum* type B,³ both type A (five cases) and type B (six cases)

disease occurred in case patients exposed to honey in this study.

Microbiological surveys of honey have found that 4% to 25% of samples contain *C botulinum* spores.²⁰⁻²² Honey should not be fed to infants younger than 1 year old, especially those younger than 6 months old.²³ One of the case patients in this study was older than 11.5 months at onset of illness. The infant was receiving breast milk, had had less than one BM per day for 6 months, and was fed a commercial honey-yogurt product during the month before developing infant botulism. Even 1-year-old infants may remain susceptible to intestinal colonization and toxin production by *C botulinum*.

An important finding of this study was that illness in infants younger than 2 months old is epidemiologically different from that in older infants. Sources of *C botulinum* spores for the youngest infants are a mystery because these infants have few environmental exposures and are rarely given foods other than breast milk and formula. Yet, almost half the reported cases of infant botulism in the United States occur in this age group. Breast-feeding was not a risk factor for this group, but living in a rural area or on a farm was associated with disease and reported by 40% of the families of case patients (Table 2). While it remains unclear how these infants came into contact with *C botulinum* or its spores, environmental contamination by this organism may be greater in rural settings.

Breast-feeding was associated with disease in infants at least 2 months old. Illness did not appear to be less severe for breast-fed infants than for non-breast-fed infants. The severity of illness tended to be greater in younger infants, whether they were breast-fed or not. Since maternal age and education and family occupational status were similar between case patients and control subjects, it is unlikely that the increased risk associated with breast-feeding was due to socioeconomic factors. The increased risk with increasing age for infant botulism among breast-fed infants suggests that factors associated with breast milk may be important. However, infant botulism is a rare disease⁶ and breast-feeding should be encouraged because its benefits far

outweigh the increased risk for infant botulism.

A unifying hypothesis that would explain the differences between infants younger than 2 months old and those 2 months of age and older is that breast-feeding may prolong susceptibility to colonization by *C botulinum*. All infants younger than 2 months old may be highly susceptible to colonization by *C botulinum* because of a poorly developed anaerobic fecal flora. Anaerobic bowel flora protect adult mice from colonization by *C botulinum*; pretreatment of the mice with metronidazole makes them receptive to colonization and the development of botulism after orogastric inoculation of *C botulinum* spores.¹⁸ Significant differences in the frequency of isolation of *Clostridium* species have been observed between breast- and bottle-fed infants.^{24,29} Extracellular factors of *Clostridium sporogenes* inhibit growth and lyse *C botulinum*.³⁰ The presence of other clostridial species may prevent intestinal colonization by *C botulinum*.

Corn syrup, like honey, is used as a sweetener for infants and to treat constipation. In a nationwide survey, spores of *C botulinum* were isolated from 0.5% of 961 bottles of corn syrup.⁷ Follow-up testing of corn syrup has continued to yield "low" levels of *C botulinum* spores.³¹ Corn syrup use was not identified as a risk factor in an earlier epidemiologic study in California.³

Odds ratios for corn syrup use in our study were elevated for all infants when analyzed in univariate and logistic regression analyses. When infants at least 2 months old were analyzed separately, the association between corn syrup use and development of infant botulism was significant. Corn syrup use was greatest for case patients who had at least one BM per day. This suggests that the increased risk for infant botulism among infants receiving corn syrup is not confounded by the use of corn syrup to treat infants with decreased BM frequency. The data are inconclusive, and additional studies are necessary to determine if the use of corn syrup is a risk factor for infant botulism.

Prevention of some cases of infant botulism may be possible through more extensive educational campaigns discouraging the use of honey. Since 11

(79%) of 14 honey products consumed by case patients and control subjects in this study were from commercial sources, use of warning labels on epidemiologically and microbiologically implicated food items may help prevent feeding of these items to infants.

The majority of cases, however, will not be prevented by these measures. Awareness of this disease and its risk factors by physicians will continue to be important to ensure early supportive care and to prevent death. The diagnosis of infant botulism was considered to be early in most patients enrolled in this study; two had mild symptoms and were not hospitalized. Many of the responsible physicians had previously cared for infants with this rare disease. However, many cases may escape diagnosis.

All afebrile infants who develop decreased ability to feed and in whom no other infectious cause is identified should have stool specimens submitted for culture of *C botulinum* and detection of toxin, particularly if there has been a change toward a less frequent BM pattern.

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Neurofibromatosis Type 1 (Recklinghausen's Disease)

Neurologic and Cognitive Assessment With Sibling Controls

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• Neurologic and cognitive function in neurofibromatosis type 1 (NF1) were assessed in a controlled pilot study of 13 pairs of siblings aged 6 to 27 years. One subject in each pair was affected with NF1, and the other, the control subject, was unaffected. Subjects with evidence of focal central nervous system disease were excluded. The 13 subjects with NF1 had no excess of mental retardation, attention-deficit disorder, or specific learning disorders (using Wilcoxon's Signed Rank Test and McNemar's Test for Symmetry). These subjects, however, had significantly higher scores for subtle neurologic abnormalities (21 vs 6) and significantly lower full-scale IQ scores (94 vs 105) than their unaffected siblings. The IQ scores of the affected subjects were not clustered at the lower end of the scale but showed a slight downward shift in distribution compared with those of their siblings. In addition, a visual-spatial orientation deficit was present in eight of nine affected subjects so evaluated. The findings suggest that subjects with NF1 have a widespread alteration of the brain during development that manifests as one or more specific types of neuropsychologic deficits.

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Neurofibromatosis type 1 (NF1), also known as Recklinghausen's disease, is one of the most common single-gene disorders of the human nervous system; it affects approximately 100 000 people in the United States.¹ The disease is characterized by café au lait spots, neurofibromas of the skin, and iris hamartomas (Lisch nodules).² The skeletal, central nervous, and endocrine systems may also be involved. Cognitive dysfunction and other developmental disabilities are said to occur in as many as 40% of patients,^{3,7} but there has been no rigorous, controlled neuropsychologic assessment of this issue.

This article describes a pilot study designed to assess subtle neurologic abnormalities, impaired cognitive function, and developmental disabilities in NF1, with the use of unaffected siblings as controls.

SUBJECTS AND METHODS Study Population

Subjects with NF1 and unaffected sibling controls for each were sought by mailing a letter to 350 local families known to the Interinstitute Medical Genetics Clinic at the Warren Grant Magnuson Clinical Center, National Institutes of Health, Bethesda, Md, and the Neurofibromatosis Clinic at Children's Hospital National Medical Center and the Metropolitan Washington Chapter of the National Neurofibromatosis Foundation, Washington, DC. With their informed consent, potential subjects and available first-degree relatives were screened by physical and neurologic examination, including ophthalmologic and audiologic evaluations. According to criteria modified from Winter et al,^{2,8} affected subjects had to have at least two of the following signs of NF1, which could not be explained by another disease process: (1) at least five café au lait spots 0.5 cm or greater in diameter if prepubertal and

at least six café au lait spots 1.5 cm or greater in diameter if older, (2) at least two cutaneous or subcutaneous lumps suggestive of neurofibromas, (3) biopsy-proved neurofibroma, (4) axillary or inguinal freckling, (5) Lisch nodules of the iris, (6) characteristic bone abnormality, such as pseudoarthrosis of the tibia or fibula, and (7) an affected parent or sibling, diagnosed by the aforementioned criteria.

Siblings were excluded as controls if they had any of the following: (1) one or more café au lait spots 0.5 cm or greater in diameter if prepubertal or 1.5 cm or greater in diameter if older, (2) one or more cutaneous or subcutaneous lumps, (3) axillary or inguinal freckling, (4) Lisch nodules of the iris, and (5) any bone abnormality characteristic of NF1. In a sibship in which there were two or more siblings who met the criteria for controls, we selected the sibling who was of the same sex as the subject and closest in age.

To avoid selection bias, affected subjects were excluded if the presence of a documented or suspected developmental disability, such as dyslexia, led to the diagnosis of NF1. To avoid confounding factors, affected subjects and sibling controls were excluded if there was evidence by medical history or cranial computed tomography (CT) of a neuropathologic process, such as epilepsy or brain tumor, or if the subject was taking medication on a long-term basis for any reason.

Assessment

Neurologic function was assessed by the Physical and Neurological Examination for Subtle Signs (PANESS),⁹ which is divided into the following five sections: (1) subtle neurodevelopmental abnormalities in gross and fine-motor function, (2) overflow phenomena, (3) sensory function, (4) handedness, and (5) tasks such as walking 10 paces heel to toe, rapid tongue wiggling, and hopping on one foot up to 30 times. These tasks were performed by all subjects in the same order and were evaluated and scored by the same observer. The PANESS was scored

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From the Neuroepidemiology Branch (Drs Eldridge, Bien, and Myers), the Developmental and Metabolic Neurology Branch (Dr Denckla), the Audiology Clinic (Ms Pikus), and the Biometry and Field Studies Branch (Dr Dambrosia), National Institute of Neurological Disorders and Stroke; the Clinical Branch, National Eye Institute (Dr Kaiser-Kupfer); the Interinstitute Medical Genetics Clinic, Warren Grant Magnuson Clinical Center (Ms Schlesinger); the Clinical Epidemiology Branch, National Cancer Institute (Drs Parry and Mulvihill); and the Human Genetics Branch, National Institute of Child Health and Human Development (Dr Zasloff), National Institutes of Health, Bethesda, Md.

Reprints not available.

from 0 (normal) to 5 (markedly abnormal). The neurologic assessment was completed in 20 to 30 minutes.

Neuropsychologic function was assessed by the Visual-Motor Integration Test,¹⁰ the Facial Recognition Test,¹¹ and the Iowa Judgment of Line Orientation Test.¹¹ Developmental disabilities involving cognitive function were evaluated by the tests and diagnostic criteria shown in Table 1. The IQ test selected for each subject was determined by the age range for which it was normalized. The Iowa Judgment of Line Orientation Test was not administered to subjects younger than 8 years of age, since normative data are not available for this age group. Each sibling of a pair was tested in the same room and at the same time on consecutive days. The tester had no knowledge of which sibling was affected, but no attempt was made to mask the features of NF1. The neuropsychologic and cognitive testing was completed in approximately 2½ hours.

Statistical Analysis

The Wilcoxon Signed Rank Test²² was used to compare the neurologic and cognitive function assessments of the affected subjects and sibling controls, and McNemar's Symmetry Test^{23,24} was used to compare their neuropsychologic function.

RESULTS

There were 91 responses to the 350 letters. The responses yielded 31 sibling pairs of presumed affected subjects and presumed unaffected siblings, aged 6 to 27 years. Eighteen of these pairs were excluded for the following reasons: the presumed affected sibling was initially referred for a learning disability (5 pairs); at least one sibling had a neurologic disorder, such as epilepsy or optic glioma (6 pairs); one or both siblings were unavailable during the study period (2 pairs); a diagnosis of NF1 could not be confirmed in the presumed affected sibling (2 pairs); or the presumed unaffected sibling had one or more café au lait spots (3 pairs). The remaining 13 pairs of siblings formed the sample for this pilot study.

Table 2 gives the clinical features of the 13 sibling pairs. The affected member of each pair is listed first. Abbreviated pedigrees indicate the status of first-degree relatives with respect to NF1 and developmental disabilities. Seven sibling pairs were of the same sex. With the exception of the siblings of pair 5, who were black American, all sibling pairs were white. The affected

Table 1.—Definition of Developmental Disabilities		
Diagnostic Category	Test or Rating Instrument	Diagnostic Criteria or Threshold
Low cognitive function	Wechsler Intelligence Scale for Children—Revised (WISC-R) ¹² and Wechsler Adult Intelligence Scale—Revised (WAIS-R) ¹³	Full-scale IQ <80: 70-79 indicates borderline mental retardation; 50-69, mild mental retardation
Spoken language disorder	Boston Naming Test, ¹⁴ Clinical Evaluation of Language Function, ¹⁵ and Token Test ¹⁶	>1 SD below mean for age
Reading disability (dyslexia)	WISC-R or WAIS-R, Gray Oral Reading Test (GOR), ¹⁷ Wide-Range Achievement Test (WRAT), ¹⁸ and Grade Equivalent Reading Level	Full-scale IQ 80-114, reading scores not at grade level, and reading quotient (RQ) <80 (RQ indicates reading age* divided by mental age); or Full-scale IQ ≥115 and RQ <80 (RQ indicates reading age divided by chronologic age)
Other learning disability	WRAT—Math and WRAT—Spelling	Math quotient (MQ) or spelling quotient (SQ) <0.80 (MQ or SQ as for RQ above)
Attention-deficit disorder	Examiner's Rating, Conner's Rating Scale for Parents, ¹⁹ Halstead-Reitan Trails, A/B Subtest, ²⁰ Digits Forward for Age, Digits Backward for Age, Cancellation of Repeated Target Symbols, and Performance Tests "592" and "LIF" ²¹	Four or more "fail-for-age" points (range, 0-9 points)† as sum of failures across ratings and tests

*Reading age was derived from the mean of GOR and WRAT, unless GOR was at or above the expected grade-equivalent reading level, in which case the GOR value was used as the reading age.

†Point range is as follows: Examiner's Rating, 0-1; Parent's Rating, 0-2; Trails, 0-1 for each of two tests; Digits Forward, 0-1; Digits Backward, 0-1; "592," 0-1; and "LIF," 0-1. This definition, developed for research purposes, is more stringent in its addition of assessment observations than are *DSM-III* or *DSM-III-R* criteria and was based on consultations with Judith Rapoport, MD, Chief, Child Psychiatry Branch, National Institute of Mental Health, Bethesda, Md.

member of pair 7 had had pseudoarthrosis of the tibia, and the affected member of pair 12 had asymmetry of the jaw. The head circumference of the affected siblings tended to be large; it was at or above the 90th percentile in 8 of the subjects. Only in pair 8 was the head circumference of the unaffected sibling relatively larger than that of the affected sibling. Probable or possible developmental disabilities, including non-right-handedness,²⁵ were present in first-degree relatives without neurofibromatosis in 10 of the 13 families.

There was a significant difference ($P<.0001$, Wilcoxon's Signed Rank Test) in the mean total score (\pm SD) on the PANESS between affected subjects (21.5 ± 12.3) and controls (5.6 ± 3.6), with a median of 16 and 5, respectively (Figure). On average, affected subjects showed more abnormalities than controls on all five sections of the examination, but motor abnormalities involving station, balance, and gait accounted for nearly two thirds of the total score of the affected subjects.

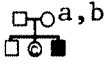

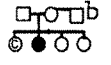
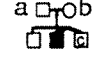

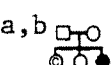
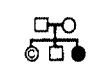
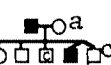

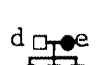
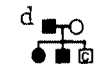
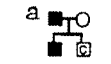
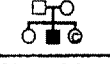
There was also a significant difference ($P<.0001$, Wilcoxon's Signed Rank Test) in mean full-scale IQ

score (\pm SD) between affected subjects (93.9 ± 11.7) and controls (105 ± 13.8), with a median of 96 and 104, respectively (Figure). The IQ scores of the affected subjects were not clustered in the subnormal range but tended to be slightly but consistently shifted downward compared with the scores of the unaffected siblings. With the exception of pair 1, the controls scored higher than the affected subjects on the verbal and performance IQ test (Table 2). The affected sibling of pair 1 was a 10-year-old boy with mathematical skills in the normal range, but his 16-year-old unaffected sister met the criteria for a specific learning disability in mathematics.

Five of the affected subjects underwent CT scanning of the brain. The affected member of pair 9, who scored the highest for neurologic abnormalities, had a normal CT scan, and none of the other scans showed changes suggestive of a tumor or dilated ventricles.²⁶

Only one of the three measures of neuropsychologic function distinguished affected subjects from controls, namely, the Iowa Judgment of Line Orientation Test. In this test of visual-spa-

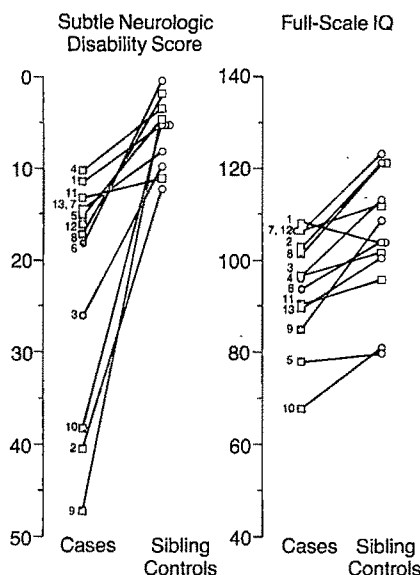
Table 2.—Clinical Features, Family History, IQ, and Developmental Disabilities*

Pair Sex/Age, y	Clinical Features					Family History	IQ			Parent's Employ- ment Code	Developmental Disability
	Café au Lait Spots	Neuro- fibromas	Freck- ling†	Lisch Nodules‡	Head Size, Percentile		Verbal	Per- formance	Full Scale		
1 M/10 F/16	>6 0	0 0	Yes No	Yes No	>97 >97		105 94	111 117	108 104	3	None OLD (M)
2 M/6 F/8	>6 0	3 0	No No	No No	90-97 25-50		101 115	106 121	103 121	3	None None
3 F/6 F/8	>6 0	0 0	Yes No	? No	25-50 25-50		98 106	93 120	96 113	4	None None
4 M/27 M/27	>6 0	>10 0	Yes No	Yes No	>97 50-75		90 98	106 108	96 102	2	Dyslexia, OLD (M,S) OLD (M,S)
5 M/20 F/15	>6 0	2 0	No No	No No	>97 75-90		77 79	85 85	78 80	6	Low cognitive function, non-R, and possible ADD Non-R, OLD (M), possible SLD, and possible ADD
6 F/13 F/18	>6 1 (<1 cm)	1 0	Yes No	? No	75-90 75-90		84 101	108 106	94 104	2	Dyslexia, non-R, and OLD (M,S) Dyslexia and OLD (M,S)
7 F/10 F/14	>6 0	0 0	Yes No	Yes No	75 50-75		107 119	102 121	105 123	5	Dyslexia, non-R, and OLD (S) None
8 M/10 M/12	>6 0	1 0	Yes No	Yes No	75-90 90		95 113	109 126	101 121	3	Dyslexia, OLD (M,S), and possible SLD Non-R
9 M/7 F/14	>6 0	1 0	Yes No	No No	75-90 75-90		96 109	75 106	85 109	1	Possible SLD None
10 M/10 F/12	>6 0	4 0	No No	Yes No	>97 50-75		62 78	75 88	68 81	7	Low cognitive function, non-R, and possible ADD Possible SLD
11 M/16 M/14	>6 0	1 0	Yes No	Yes No	>97 75-90		92 86	91 108	91 96	4	OLD (M,S) and possible ADD ADD and OLD (M,S)
12 M/21 M/19	>6 0	0 0	Yes No	Yes No	>97 25-50		96 101	118 124	106 112	1	Non-R and OLD (M,S) Dyslexia and OLD (S)
13 M/14 F/12	>6 1 (<0.3 cm)	0 0	Yes No	? No	90-97 25-50		88 103	93 98	90 101	3	Non-R and OLD (M) Possible SLD

*Non-R indicates non-right-handed; ADD, attention-deficit disorder; OLD (M,S), other learning disorder (mathematics and spelling); and SLD, spoken language disorder. For family history (pedigree), a solid square or circle indicates an affected person, and a c within a square or circle indicates a control subject; an a indicates non-R; b, possible dyslexia; c, possible ADD; d, OLD; and e, probable dyslexia. Pair 4 includes fraternal twins. Parent employment codes are as follows: 1 indicates professional and 7, laborer.

†In axillary or inguinal areas.

‡Question mark indicates an inconclusive examination.



Subtle neurologic disability and full-scale IQ in 13 subjects with neurofibromatosis type 1 (Recklinghausen's disease) and 13 unaffected sibling controls. Solid symbols indicate affected subjects; open symbols, unaffected subjects; squares, males; and circles, females. Number in relation to symbol is the number of the sibling pair as listed in Table 2. Vertical axis on the left is the neurologic disability score, as determined by total number of points on the Physical and Neurological Examination for Subtle Signs⁹ of developmental neurologic abnormalities.

tial ability, the subject predicts the angle that would be produced if two separate lines were to intersect. The test was performed by the nine sibling pairs who were at least 8 years old, the minimum age for which the test is normalized. Eight affected subjects and one unaffected subject scored in the deficient range ($P < .025$, McNemar's Symmetry Test plus correction factor), and one affected subject scored in the superior range.

Actual or suspected developmental disabilities involving cognitive function were found in 10 affected subjects and 8 controls (Table 2). The affected subjects had no apparent excess of low cognitive function, specific learning disorders, or attention-deficit disorder compared with their sibling controls. Because most learning disabilities show a male preponderance,²⁶ we inspected the results for males with NF1 and male controls. Among the 10 males with NF1, there were 2 subjects with dyslexia, 5 subjects with other learning disorders, and 3 subjects with possible attention-deficit disorder. Among 4 male controls,

there was 1 subject with dyslexia, 3 with other learning disorders, and 1 with attention-deficit disorder.

COMMENT

Reduced cognitive function did not seem to be present in either of the two subjects described in Von Recklinghausen's original report.²⁷ About subject 1, he commented, "Apart from a great attraction to the male sex, she exhibited nothing unusual in her mental sphere"; and of subject 2, he noted, "His intelligence did not seem exceptional, nor on the other hand below average." Subsequent reports, however, often mentioned an association between Recklinghausen's disease and reduced cognitive function.

In the extensive Michigan study,⁴ in which patients with neurofibromatosis were ascertained from multiple medical sources, a mean IQ of 45 was found in 20 institutionalized patients compared with a mean IQ of 77 in 15 of 203 noninstitutionalized patients for whom such data were available. In patients with neurofibromatosis ascertained through Australian hospitals,³ mental retardation was reported in 11 (14%) of 78 children. A later study⁷ suggested that other developmental disabilities are also common in this disorder.

A review of previous studies showed one or more of the following limitations: (1) minimal criteria for the diagnosis of NF1 were not stated, and subjects with other conditions sharing some features of this form of neurofibromatosis, such as bilateral acoustic neurofibromatosis (NF2), may have been included; (2) the presence of a focal neurologic process that could produce a selective neurologic or cognitive defect was not ruled out; (3) the selection of subjects was probably biased toward those with neurologic and cognitive handicaps since, in most studies, subjects were ascertained through hospitals rather than population sampling; and (4) the results of subjects were compared with historical values from the general population rather than with results from concurrent controls, without regard to social and environmental factors that can influence intelligence and educational achievement.²⁸

Perhaps because the current study specifically addressed the limitations of

previous studies, it was able to identify consistent neurologic and cognitive alterations in NF1. In addition, because the study was conducted at one center, all 13 sibling pairs were assessed by the same investigators. Nevertheless, our study has its limitations, one of which is the likelihood of bias in ascertaining families with suitable sibling pairs. Subjects were recruited by a letter describing the neurologic and neuropsychologic focus of the study, and families with children perceived to have problems in these realms may have been more likely than others to respond. To overcome this tendency, we excluded the five subjects in whom evaluation for a developmental disability led to the diagnosis of NF1. Also, some controls who had no clinical signs or symptoms of the disease may still carry the NF1 gene, which will become manifest later; however, in a previous survey,²⁹ all affected children exhibited some skin manifestations by age 5 years.

Another possible criticism of our study is that an intracranial mass or other focal neurologic process could have been missed in any of the eight subjects with NF1 who did undergo CT scanning. Furthermore, neuropsychologic testing took as long as 2½ hours, which required considerable motivation of the subjects, particularly for the young ones and those with attention-deficit disorder. Still, the tester had 10 years of experience in testing young age groups.

It is also possible that the developmental disabilities in our study occurred to excess in the relatives who did not have NF1. If NF1 is associated with developmental disability and if assortative mating for such dysfunction exists, developmentally disabled persons may be more likely to mate with other developmentally disabled persons. However, our use of sibling controls with the same biologic parents as affected subjects should permit distinction between developmental disabilities resulting from familial influences and those attributable to the NF1 gene itself.

A final limitation of our study is the small sample size. Because of the rigorous selection criteria, only 13 sibling pairs from the initial sample of 31 pairs were tested. Thus, only large differences would achieve statistical signifi-

cance. In each sibling pair, the affected member had more neurologic abnormalities than did the unaffected member. The abnormalities were subtle and chiefly involved axial coordination, station, and gait. The instrument employed, the PANESS, did not discriminate absolutely between affected and unaffected subjects, since some unaffected ones had a slightly higher examination score than some with NF1. Although the significance of subtle neurologic signs involving voluntary movements has been debated,³⁰ their reproducibility has recently been validated,³¹ and their usefulness as predictors of such neurologic disorders as Huntington's disease has been demonstrated.³²

Although the mean full-scale IQ score was significantly lower in the siblings with NF1, a specific cognitive deficit did not seem to be a factor. However, affected males tended to score higher on the performance IQ scale than on the verbal IQ scale (seven scored higher, one scored lower, and one scored equal on both scales). In addition, the neurologic assessment score did not predict the full-scale IQ score for affected subjects.

Alteration in visual-spatial function may be a feature of NF1, and one with clinical consequences. This finding was the only major neuropsychologic abnormality in our study and was also in a recent study of children attending a learning disorders clinic,³³ in which related test instruments demonstrated visual-motor disability in 12 (56%) of 23 children with NF1 but in only 18 (6%) of 297 clinic controls.

Although certain neurologic deficiencies and one specific cognitive deficit were characteristic of NF1, the affected subjects had no significant excess of cognitive developmental disabilities (Table 1) compared with their unaffected siblings. Of the 10 affected siblings who had one or more developmental disabilities, 6 were not right-handed. Of the 13 unaffected siblings, 2 were not right-handed and 8 had one or more developmental disabilities. In all, 30 of 64 persons in these 13 families had clinical evidence of developmental disabilities. This frequency appears high, but addi-

tional studies are needed for clarification. There also does not seem to be a specific developmental disability that is characteristic of NF1.

What underlies the mild but consistent neurologic and cognitive alterations? The one relevant study,³⁴ an autopsy report, compared the brains from 10 adults with NF1 and 5 controls. Some brains from those with NF1 had abnormal collections or nests of neurons deep in the white matter, as well as distorted cortical architecture with polymicrogyria and abnormal cortical layering, perhaps resulting from abnormal migration of precursor neuronal cells from the neural crest. Further evidence for widespread alteration of the brain in NF1 comes from the observation of our study and others⁶ that head circumference is often increased.

Mary Ann Wilson, chapter president, and the members of the Metropolitan Washington Chapter of the National Neurofibromatosis Foundation encouraged this study and participated in it, and Kenneth Rosenbaum, MD, provided the families who were attending the Neurofibromatosis Clinic at Children's Hospital National Medical Center. B. J. Hessie and Carolyn Collins provided editorial assistance.

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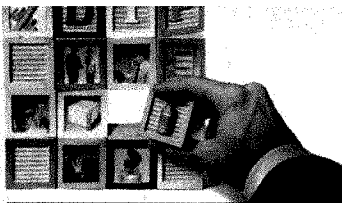
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Before prescribing, please consult the complete package circular.

INDICATIONS AND USAGE: For active immunization of infants and children to age 7 years against diphtheria, tetanus and pertussis (whooping cough) simultaneously. DTP is recommended for primary immunization of infants and children up to 7 years of age. However, in instances where the pertussis vaccine component is contraindicated, or where the physician decides that pertussis vaccine is not to be administered, Diphtheria and Tetanus Toxoids Adsorbed (For Pediatric Use) should be used. Immunization should be started at 6 weeks to 2 months of age and be completed before the seventh birthday.

CONTRAINDICATIONS: Persons 7 years of age and older must NOT be immunized with Pertussis Vaccine.

Absolute contraindications.

1. Allergic hypersensitivity to any component of the vaccine.
2. Fever of 40.5°C (105°F) or greater within 48 hours.
3. Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
4. Persisting, inconsolable crying lasting 3 hours or more or an unusual, high-pitched cry occurring within 48 hours.
5. Convulsion(s) with or without fever occurring within 7 days.
6. Encephalopathy occurring within 7 days; this includes severe alterations in consciousness with generalized or focal neurologic signs.

The presence of a neurologic condition characterized by changing developmental or neurologic findings, regardless of whether a definitive diagnosis has been made, is also considered an absolute contraindication to receipt of pertussis vaccine, because administration of DTP may coincide with or possibly even aggravate manifestations of the disease. Such disorders include uncontrolled epilepsy, infantile spasms, and progressive encephalopathy.

Use of this product is also contraindicated if the child has a personal or family history of a seizure disorder. However, the ACIP does not accept family histories of convulsions or other central nervous system disorders as contraindications to pertussis vaccination.

IT IS ALSO A CONTRAINDICATION TO ADMINISTER DTP TO INDIVIDUALS KNOWN TO BE SENSITIVE TO THIMEROSAL. IN ANY CASE, EPINEPHRINE INJECTION (1:1000) MUST BE IMMEDIATELY AVAILABLE SHOULD AN ACUTE ANAPHYLACTIC REACTION OCCUR DUE TO ANY COMPONENT OF THE VACCINE.

Elective immunization procedures should be deferred during an outbreak of poliomyelitis.

WARNINGS: This vaccine must NOT be used for immunizing persons 7 years of age and older.

IMMUNIZATION SHOULD BE DEFERRED DURING THE COURSE OF ANY ACUTE ILLNESS. THE OCCURRENCE OF ANY TYPE OF NEUROLOGICAL SYMPTOMS OR SIGNS, INCLUDING ONE OR MORE CONVULSIONS (SEIZURES) FOLLOWING ADMINISTRATION OF THIS PRODUCT IS AN ABSOLUTE CONTRAINDICATION TO FURTHER USE. USE OF THIS PRODUCT IS ALSO CONTRAINDICATED IF THE CHILD HAS A PERSONAL OR FAMILY HISTORY OF A SEIZURE DISORDER.

THE PRESENCE OF ANY EVOLVING OR CHANGING DISORDER AFFECTING THE CENTRAL NERVOUS SYSTEM IS A CONTRAINDICATION TO ADMINISTRATION OF DTP REGARDLESS OF WHETHER THE SUSPECTED NEUROLOGICAL DISORDER IS ASSOCIATED WITH OCCURRENCE OF SEIZURE ACTIVITY OF ANY TYPE.

The administration of DTP to children with proven or suspected underlying neurological disorders, must be decided on an individual basis. Please refer to ACIP recommendations for the following categories of patients:

1. Infants as yet unimmunized who are suspected of having underlying neurologic disease.
2. Infants and children with neurologic events temporally associated with DTP.
3. Incompletely immunized children with neurologic events occurring between doses.
4. Infants and children with stable neurologic conditions.
5. Children with resolved or corrected neurologic disorders.

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. Short-term (less than 2 weeks) corticosteroid therapy or intra-articular, bursal, or tendon injections with corticosteroids should not be immunosuppressive. Although no specific studies with pertussis vaccine are available, if immunosuppressive therapy will be discontinued shortly, it would be reasonable to defer immunization until the patient has been off therapy for one month, otherwise, the patient should be vaccinated while still on therapy.

Persons receiving immunosuppressive therapy, a recent injection of immune globulin, or having an immunodeficiency disorder, may not generate an adequate immunologic response to the DTP vaccine.

DTP should not be given to infants or children with any coagulation disorder that would contraindicate intramuscular injection, unless the potential benefit clearly outweighs the risk of administration.

The simultaneous administration of DTP, oral polio virus vaccine (OPV), and/or measles-mumps-rubella vaccine (MMR) has resulted in seroconversion rates and rates of side effects similar to those observed when the vaccines are administered separately. Please refer to ACIP recommendations.

PRECAUTIONS

GENERAL

Epinephrine injection (1:1000) must be immediately available should an acute anaphylactic reaction occur due to any component of the vaccine.

Prior to an injection of any vaccine, all known precautions should be taken to prevent side reactions. This includes a review of the patient's history with respect to possible sensitivity and any previous adverse reactions to the vaccine or similar vaccines (see CONTRAINDICATIONS), and a current knowledge of the literature concerning the use of the vaccine under consideration.

The vial of vaccine should be vigorously shaken to ensure a proper suspension of the antigen and adjuvant.

Special care should be taken to ensure that the injection does not enter a blood vessel.

A separate sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another.

ADVERSE REACTIONS

Not all adverse events following administration of DTP are causally related to DTP vaccine.

Adverse reactions which may be local and include pain, erythema, heat, edema and induration with or without tenderness, are common after the administration of vaccines containing diphtheria, tetanus, or pertussis antigens. Some data suggest that febrile reactions are more likely to occur in those who have experienced such responses after prior doses. However, these observations were not noted by Barkin, R.M., et al. Occasionally, a nodule may be palpable at the injection site of adsorbed products for several weeks. Sterile abscesses at the site of injection have been reported (6-10 per million doses).

Mild systemic reactions, such as fever, drowsiness, fretfulness, and anorexia, occur quite frequently. These reactions are significantly more common following DTP than following DT, are usually self-limited, and need no therapy other than, perhaps, symptomatic treatment (e.g., antipyretics). Rash, allergic reactions, and respiratory difficulties, including apnea, have been observed.

Moderate to severe systemic events, such as fever of 40.5°C (105°F) or higher, persistent, inconsolable crying lasting 3 hours or more, unusual high-pitched crying, collapse, or convulsions, occur relatively infrequently. More severe neurologic complications, such as a prolonged convulsion or an encephalopathy, occasionally fatal, have been reported to be associated with DTP administration.

Approximate rates for adverse events following receipt of DTP vaccine (regardless of dose number in the series) are indicated in Table 1.

TABLE 1. Adverse events occurring within 48 hours of DTP immunizations

Event	Frequency*
Local	
Redness	1/3 doses
Swelling	2/5 doses
Pain	1/2 doses
Mild/moderate systemic	
Fever >38°C (100.4°F)	1/2 doses
Drowsiness	1/3 doses
Fretfulness	1/2 doses
Vomiting	1/15 doses
Anorexia	1/5 doses
More serious systemic	
Persistent, inconsolable crying (duration ≥3 hours)	1/100 doses
High-pitched, unusual cry	1/900 doses
Fever ≥40.5°C (≥105°F)	1/330 doses
Collapse (hypotonic-hyporesponsive episode)	1/1,750 doses
Convulsions (with or without fever)	1/1,750 doses
Acute encephalopathy†	1/110,000 doses
Permanent neurologic deficit†	1/310,000 doses

*Number of adverse events per total number of doses regardless of dose number in DTP series. †Occurring within 7 days of DTP immunization.

The frequency of local reactions and fever following DTP vaccination is significantly higher with increasing numbers of doses of DTP, while other mild to moderate systemic reactions (e.g., fretfulness, vomiting) are significantly less frequent. If local redness of 2.5 cm or greater occurs, the likelihood of recurrence after another DTP dose increases significantly.

Although there are uncertainties in the reported studies, recent data suggest that infants and young children who have had previous convulsions (whether febrile or nonfebrile) are more likely to have seizures following DTP than those without such histories.

Rarely, an anaphylactic reaction (i.e., hives, swelling of the mouth, difficulty breathing, hypotension, or shock) has been reported after receiving preparations containing diphtheria, tetanus, and/or pertussis antigens.

Sudden infant death syndrome (SIDS) has occurred in infants following administration of DTP. A large case-control study of SIDS in the United States showed that receipt of DTP was not causally related to SIDS. It should be recognized that the first three primary immunizing doses of DTP are usually administered to infants 2-6 months old and that approximately 85% of SIDS cases occur at ages 1-6 months, with the peak incidence occurring at 6 weeks-4 months of age. By chance alone, some SIDS victims can be expected to have recently received vaccine.

Onset of infantile spasms has occurred in infants who have recently received DTP or DT. Analysis of data from the NCEs on children with infantile spasms showed that receipt of DTP or DT was not causally related to infantile spasms. The incidence of onset of infantile spasms increases at 3-9 months of age, the time period in which the second and third doses of DTP are generally given. Therefore, some cases of infantile spasms can be expected to be related by chance alone to recent receipt of DTP.

Reporting of Adverse Events

Reporting by parents and patients of all adverse events occurring within 4 weeks of antigen administration should be encouraged.

The following illnesses have been reported as temporally associated with the vaccine; neurological complications including cochlear lesion, brachial plexus neuropathies, paralysis of the radial nerve, paralysis of the recurrent nerve, accommodation paresis, and EEG disturbances with encephalopathy. In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid, tetanus toxoid should be considered as a possible etiology.

Product information as of July, 1986



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Radiological Case of the Month

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Irwin Rappaport, MD (*Contributors*); Beverly P. Wood, MD (*Section Editor*)

A 10-year-old girl was brought to the pediatric emergency department after a falling 120 × 240-cm sheet rock pinned her chest against a wall. She complained of chest pain and coughed up a teaspoonful of bright-red sputum. Her respiratory rate was 22/min. She

had no fever or cyanosis. The physical examination was remarkable only for mild ecchymosis and costochondral tenderness over the right infraclavicular region and decreased breath sounds over the anterior right upper portion of the chest. Her history and family history were normal. Her growth and development were normal. She has always resided in New York City, with the exception of a 1-month visit to Ecuador 6 years earlier. There was no known exposure to tuberculosis or other infection.

A chest roentgenogram was obtained in the emergency department

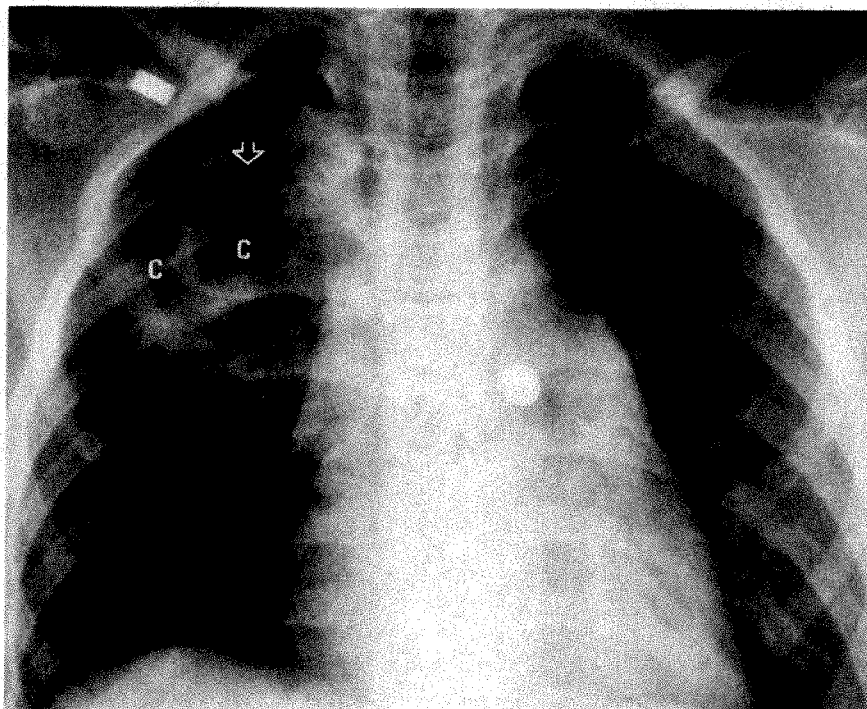
(Fig 1) and a computed tomographic examination was performed the following day (Fig 2). Results of a complete blood cell count and arterial blood gas and liver function test results were normal. Creatine phosphokinase level was initially elevated to 275 U/L (100% CK-MM). Purified protein derivative was nonreactive, but her father developed a 20-mm induration in 48 hours. The father's chest roentgenogram was normal. Sputum or blood cultures yielded no pathogens. No acid-fast bacilli were found in bronchial washings and none grew in the subsequent cultures.

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Figure 1.



Denouement and Discussion

Traumatic Pulmonary Pseudocyst

Fig 1.—Two cavities (C) and surrounding areas of increased density are present in the right upper lobe. The wall of the larger and medially located cavity is mostly thin (arrow). The inner surfaces of the cavities are smooth.

Fig 2.—Top, Computed tomographic scan at the level of the aortic arch shows two cavities (C) in the right upper lobe surrounded by consolidated lung parenchyma. Mottled consolidation throughout the right upper lobe represents pulmonary contusion. Arrows indicate a small anterior pneumothorax. Bottom, Section at the right upper lobe bronchus (B) shows perihilar and posterior pulmonary parenchymal contusion and hemorrhage. Note a medially located small pneumothorax (arrow).

Fig 3.—Follow-up chest roentgenogram obtained 10 weeks later is normal.

Cavitary pulmonary lesions may result from blunt chest trauma. They are variably named pseudocysts, pseudocystic hematoma, traumatic cysts, pneumatocele, and traumatic lung cavities.¹ *Traumatic pulmonary pseudocyst* is the most widely accepted term. Eighty-five percent of reported cases occur in patients under age 30 years.^{2,3}

Patients present with mild symptoms following blunt chest trauma. Symptoms last 1 or 2 days and consist of cough and chest pain. Hemoptysis occurs in about 40% of the patients^{1,2} and is usually mild. In some cases, marked hemoptysis coinciding with evacuation of the cyst can occur. Low fever and leukocytosis have been reported and are probably related to lung injury and resorption of the hematoma.

Traumatic pseudocysts result from laceration of the lung parenchyma with elastic recoil pull acting centrifugally on the damaged lung and leakage of air from alveoli or torn bronchi-

oles.^{2,3} The resiliency of the thorax in young people is thought to be one of the most important factors contributing to the formation of traumatic lung cysts. It is theorized that the chest is rapidly compressed, then rapidly reexpands, with a decrease in the intrathoracic pressure. This effect may burst or shear the lung.³

While the clinical picture is innocuous, the radiologic findings are striking. A cavitary lesion develops quickly, and an air-fluid level is frequently present. There is usually pulmonary consolidation surrounding the cavity, producing the false appearance of a thick wall. If the cavity is completely filled with blood, a homogeneous density is seen,⁴ but the cavitary nature of the lesion becomes evident after hemoptysis and evacuation of the cyst contents. Spontaneous resolution usually occurs within 1 to 3 weeks. Cyst superinfection is reported and presents with purulent sputum, increasing pulmonary consolidation, fever, and leukocytosis.²

The roentgenographic appearance of traumatic pseudocyst may suggest lung abscess or cavitation secondary

to tuberculosis or fungal infection. Congenital adenomatoid malformation or a bronchogenic cyst may be included in the differential diagnosis. A history of recent chest trauma in an otherwise-healthy person, negative or normal skin tests and cultures, and comparison with previous chest roentgenograms are usually sufficient to exclude these possibilities. Spontaneous resolution of the lesion(s) within a few weeks further supports the diagnosis.

Traumatic pulmonary pseudocyst requires no specific treatment. Prophylactic administration of antibiotics is disputed in light of the rare occurrence of secondary infection. Surgical intervention is reserved for cases of persistent infection or significant ventilatory compromise secondary to large pseudocysts.⁵

In our patient, there was complete radiologic resolution of the cyst and absence of any clinical symptoms 10 weeks after the injury (Fig 3). Pulmonary function tests at that time revealed a decrease in diffusing capacity for carbon monoxide, suggesting related residual alveolar capillary disruption.

Figure 2.

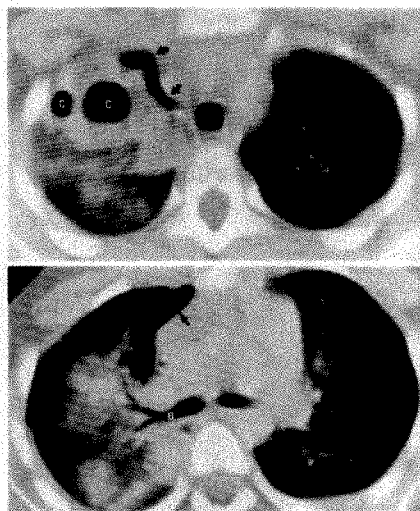
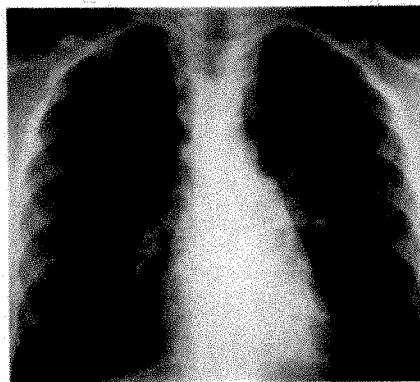


Figure 3.



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Picture of the Month

Gail J. Demmler, MD; Moise L. Levy, MD; Charles L. Cole, PhD; Clifford O. Mishaw, MD;
Arthur B. Benson, MD; Richard M. Thaller, MD (*Contributors*); Murray Feingold, MD (*Section Editor*)

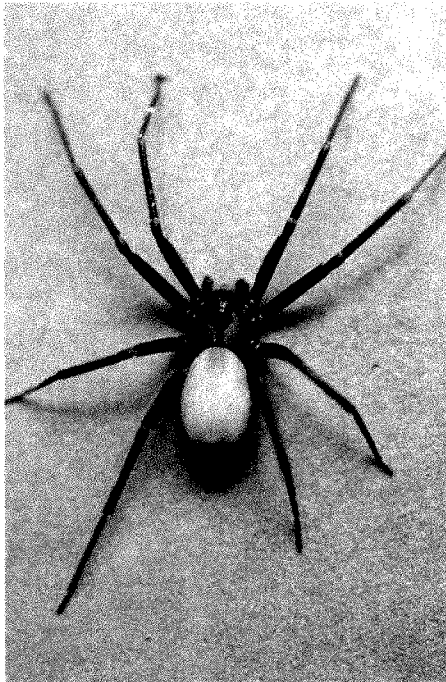


Figure 1.



Figure 2.

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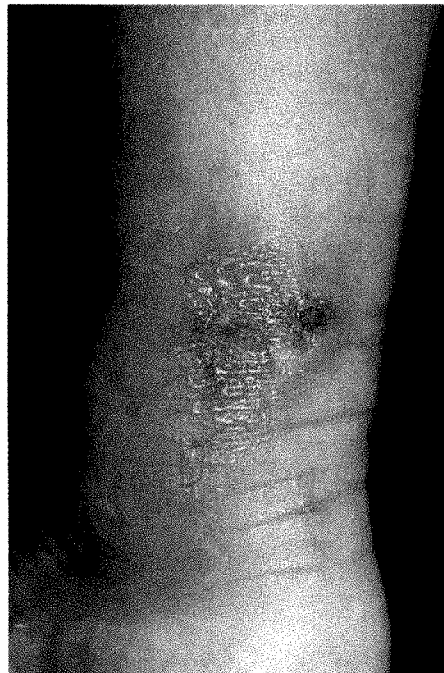


Figure 3.

Denouement and Discussion

Fig 1.—*Loxosceles reclusa*, the brown recluse spider.

Fig 2.—Bite of the brown recluse spider with local pustule, erythema, and induration.

Fig 3.—Typical bite of the brown recluse spider with local cyanotic pustule and necrosis.

The brown recluse is a medium-sized spider with rather long legs that cover an area of about the size of a quarter to a half-dollar (Fig 1). The legs and body are covered with fine hairs, and it is light to tawny brown. Most spiders have eight eyes; however, the brown recluse has only six eyes. Another distinguishing characteristic is the dark violin or fiddle-shaped marking directly above the legs on the cephalothorax.

In the United States, there are 13 species of spiders belonging to the genus *Loxosceles*. The bite of at least 4 species—*Loxosceles reclusa*, *Loxosceles deserta*, *Loxosceles laeta*, and *Loxosceles rufescens*—is associated with systemic reactions in humans. The species *L. reclusa*, commonly called the brown recluse spider, violin spider, or fiddleback spider, is by far the species most commonly associated with human bites. It inhabits many southern and midwestern states, in-

cluding Alabama, Arkansas, Georgia, Kansas, Kentucky, Louisiana, Mississippi, Missouri, Nebraska, Ohio, Oklahoma, Tennessee, and Texas.

The brown recluse is a shy, solitary spider and clusters in favorable habitats, such as under the loose bark of standing dead trees. In the home, they can be found in cellars, closets, basements, bedrooms, and bathrooms, and behind pictures, wall hangings, curtains, furniture, and appliances.

The bite of the brown recluse varies from a stinging or burning sensation to a severe systemic condition and even death. Most bites are located on the buttocks, upper thigh, or foot. They produce local pain and pruritus during the first 24 hours, and systemic signs, if they occur, are evident within 72 hours (Fig 2). The bite may become a cyanotic pustule and progress to a necrotic eschar with stellate ulceration (Fig 3). Systemic loxoscelism may be more common in children and pro-

duces a scarlatiniform rash, generalized urticaria, malaise, and fever. In some cases, vomiting and diarrhea, disseminated intravascular coagulation, shock, and death can occur. The differential diagnosis of spider bites includes bites and stings from other arthropods and insects, cellulitis, vasculitis, and pyoderma gangrenosum.

The treatment of brown recluse spider bites remains controversial. Early and delayed surgical excision, intralesional steroids, systemic steroids such as oral prednisone, ice or cold packs applied to the bite, aspirin, oral antibiotics, tetanus toxoid, and even antivenin have all been tried. Most recently, oral dapsone, an inhibitor of neutrophil function, has been used to treat severe *Loxosceles* bites.

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The Editors welcome contributions to PICTURE OF THE MONTH and RADIOLOGICAL CASE OF THE MONTH. Those who wish to contribute should send their manuscripts to Dr Feingold (Picture of the Month), National Birth Defects Center, Franciscan Children's Hospital, 30 Warren St, Brighton, MA 02135, or Dr Wood (Radiological Case of the Month), University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.

Pulse Oximetry in Methemoglobinemia

Mehernoor F. Watcha, MD, DCh; Michael T. Connor, MD; Anne V. Hing, MD

• Pulse oximetry is a major improvement in the assessment of oxygenation. The device uses plethysmography and light absorbance measurements at two wavelengths to estimate oxygen saturation. It is inaccurate, however, when more than two types of hemoglobin are present. This article describes two infants with methemoglobinemia in whom pulse oximetry overestimated oxygen saturation. We discuss the mechanism of this systematic error and emphasize that pulse oximetry should not be used to estimate true oxygen saturation in the presence of methemoglobin. However, a disparity between oxygen saturation estimates by pulse oximetry and by calculations based on the arterial partial pressure of oxygen and the oxygen-hemoglobin dissociation curve can provide an important clue to the presence of such abnormal types of hemoglobins. Therapy should be based on direct measurements of oxyhemoglobin by cooximetry and not on measurements of oxygen saturation by pulse oximetry or on saturations calculated from the P_{aO_2} and the oxyhemoglobin dissociation curve.

(AJDC. 1989;143:845-847)

Pulse oximetry is a major advance in the noninvasive monitoring of oxygen saturation. It has been quickly accepted in clinical practice because it is easy to perform, painless, rapid in response, and accurate when arterial saturations are greater than 65%.^{1,2} Unlike transcutaneous oxygen tension measurements, pulse oximetry requires no warm-up time, special skin preparation, or complex calibration. However, pulse oximetry gives an inaccurate estimate of arterial oxygen saturation (SaO_2) in the presence of dyes,³⁻⁶ abnormal types of

hemoglobins,⁷⁻¹¹ or when the saturation is below 65%.^{1,2} In this article, we describe two infants with severe acquired methemoglobinemia whose SaO_2 level was measured by pulse oximetry and cooximetry (which measured the oxyhemoglobin [HbO_2] level) and calculated from the P_{aO_2} measurements.

PATIENT REPORTS

PATIENT 1.—A 12-month-old male infant was brought to a community hospital after his mother saw an older sibling feeding him phenazopyridine hydrochloride (Pyridium) tablets, a urinary analgesic known to cause methemoglobinemia.¹² The neonate was awake, alert, and comfortable, and had normal vital signs. His nail beds and lips were cyanotic. He was treated with Ipecac, activated charcoal, and magnesium sulfate. An arterial blood sample was brown, did not change color on exposure to air, and had a methemoglobin concentration of 16%. The child then received 1.5 mg/kg of methylene blue intravenously, but 30 minutes later on arrival at St Louis (Mo) Children's Hospital, he was still cyanotic and comfortable. Another arterial blood sample was obtained, and additional methylene blue (2 mg/kg) was administered, with resolution of the cyanosis. The patient was discharged after an uneventful 48-hour hospitalization. Serial arterial blood gas analysis results, pulse oximetry readings, and HbO_2 and methemoglobin values are given in Table 1.

PATIENT 2.—A 3-week-old female neonate was admitted to St Louis Children's Hospital with a 4-day history of diarrhea, vomiting, and irritability. She was grunting and tachypneic. Her fontanelle was sunken, and her hands and feet were cold. Skin turgor and capillary refill improved after vigorous fluid resuscitation. An arterial blood sample was obtained at this point, and the results are given in Table 1 along with pulse oximetry readings. Although the P_{aO_2} level was 166 mm Hg, her blood was dark, and the SaO_2 value was only 78%. Methemoglobinemia was suspected and confirmed by cooximetry. Methylene blue (1 mg/kg) was administered intravenously. We failed to identify exposure to nitrites, nitrates, benzocaine, dyes,

or other agents known to produce methemoglobinemia.¹² Blood, urine, stool, and cerebrospinal fluid cultures did not reveal pathogens. Results of hemoglobin electrophoresis and determinations of erythrocyte glucose-6-phosphate dehydrogenase and urine amino acids were within normal limits. Urine organic acid screening revealed only lactic acid. Urine drug screens disclosed only those medications administered by health care personnel after hospital admission. Diarrhea recurred with refeeding, and poor weight gain persisted despite the administration of a monosaccharide, protein hydrolysate formula. On the 10th day, severe grunting Kussmaul respiration occurred, and methemoglobin concentrations were again elevated. Despite vigorous therapy with intravenous fluids, methylene blue, antibiotics, as well as catecholamines, tracheal intubation, and ventilation, the child lost all evidence of cerebral function and died on the 16th day. Values for arterial blood gas, cooximetry, and pulse oximetry are presented in Table 1.

COMMENT

Oxygen saturation can be directly measured by a cooximeter using spectrophotometric techniques to estimate the HbO_2 percentage of total hemoglobin concentration in a blood sample. These values are expressed either as a percentage of total hemoglobin concentration (reduced hemoglobin level + HbO_2 level + carboxyhemoglobin level + methemoglobin level) or as a percentage of hemoglobin concentration that has a capacity to bind to oxygen (HbO_2 level + reduced hemoglobin level). The former value is termed *fractional oxygen saturation* and the latter, *functional oxygen saturation*. In this article, all HbO_2 values represent the fractional oxygen saturation.

In the typical clinical blood gas laboratory, oxygen saturations are usually not measured directly but are calculated from P_{aO_2} levels and the oxygen-hemoglobin dissociation curve as corrected for the effects of temperature,

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Table 1.—Results of Arterial Blood Sample

Time at and After Admission	Oxygen Saturation*					
	Fio ₂	Pao ₂ , mm Hg	Calculated Saturation,† %	Sao ₂ , %	Hbo ₂ , % Total Hb	MethHb, % Total Hb
Case 1						
Admission	0.4	155	99.3	63	43.7	54.8
4 h	0.35	102	98	81	66.1	30.2
8 h	0.3	104	98.3	85	74.1	22.6
16 h	0.3	110	99	89	82.2	15.2
24 h	0.21	100	99	95	93.1	5.8
Case 2						
Admission	0.5	166	99	85	76.8	22.4
24 h	0.4	107	98.5	97	94.1	5.6
10 d	1.0	382	100	84	45.5	25.7
10 d, 12 h	0.5	291	100	93	85.4	12.7
11 d	0.4	179	99.7	98	96.6	2.5

*Fio₂ indicates fraction of inspired oxygen; Sao₂, arterial oxygen saturation using pulse oximetry; Hbo₂, oxyhemoglobin percentage of total hemoglobin concentration; Hb, hemoglobin; and MethHb, methemoglobin.

†Saturation of Hb calculated from the Pao₂ value and the oxygen-hemoglobin dissociation curve.

Paco₂ levels, hematocrit, and 2,3-diphosphoglycerate activity.¹⁸ Calculated oxygen saturations assume the presence of only HbO₂ or reduced hemoglobin.

In clinical situations, pulse oximetry has an advantage over these intermittent laboratory measurements, as it permits the continuous noninvasive monitoring of oxygen saturation in vivo. Although pulse oximetry has substantially improved the treatment of patients at risk for hypoxia, it has its limitations. The accuracy of pulse oximetry can be affected by patient movement,^{1,14} compression of the sensor,^{1,2,14} severe desaturation,² low perfusion states,^{1,11,14} surgical electrocautery,^{11,14} infrared heating lamps,^{1,2,7,11,14} nail polish (other than red),¹⁵ intravenous dyes,^{8,6} and abnormal types of hemoglobins.^{8,11,16}

Oxygen saturation measurements derived from pulse oximetry and cooximetry are based on Beer's law, which states that the concentration of a solute in suspension has an exponential relationship to the intensity of light that is transmitted through it.^{1,2,17} The cooximeter (IL-282) measures light absorbance at four wavelengths and uses the extinction coefficients at each wavelength to calculate the relative concentrations of HbO₂, reduced hemoglobin, carboxyhemoglobin, and methemoglobin. The pulse oximeter employs only

two wavelengths and identifies the influx of arterial blood by plethysmography. The "pulse added" absorbance signal exceeding diastolic tissue absorbance is measured at 660 and 940 nm, and the ratio is calculated by a microprocessor in the device. This ratio has been empirically correlated with oxygen saturation values obtained from invasive data in healthy adult volunteers. A ratio of 3.4, 1.0, and 0.43 correlates with oxygen saturation readings of 0%, 85%, and 100%, respectively.^{1,10,11,17} An increase in the 660- to 940-nm light absorbance ratio is interpreted by the pulse oximeter as a fall in oxygen saturation.

Pulse oximetry (Sao₂) values are not affected by differences in skin pigmentation, total hemoglobin concentration, or thickness of the tissue at the site of monitoring.^{1,2,7,11,17} However, the two-wavelength system does not allow the device to differentiate between more than two types of hemoglobin (HbO₂ and reduced hemoglobin). If another form of hemoglobin is present, pulse oximetry readings may correlate poorly with cooximetry values of HbO₂.^{7,8} In carbon monoxide poisoning, pulse oximetry gives higher readings than the true HbO₂ levels by cooximetry and consequently fails to alert the physician to potentially lethal hypoxia.⁸

Theoretical considerations suggest

Table 2.—Extinction Coefficients of Hemoglobin Derivatives*

Wavelength	660 nm	940 nm
Oxyhemoglobin (adult)	0.08	0.30
Reduced hemoglobin (adult)	0.8	0.20
Carboxyhemoglobin	0.07	0.02
Methemoglobin	0.81	0.64
Fetal oxyhemoglobin	0.09	0.34
Fetal reduced hemoglobin	0.91	0.20

*Optical density of an absorber in a concentration of 1 mmol/L measured with a path length of 1 cm.

that methemoglobin will also affect Sao₂ readings. Methemoglobin is formed by converting iron in hemoglobin to the ferric state in which it cannot bind to oxygen. This form of hemoglobin absorbs more light at both 660 and 940 nm than does HbO₂ or reduced hemoglobin but has a disproportionately greater absorbance at 660 nm (Table 2). The result, an increase in the 660- to 940-nm absorbance ratio, is interpreted by the pulse oximeter as a reduction in oxygen saturation. When 65% or more of the total hemoglobin concentration is in the methemoglobin form, the 660- to 940-nm light absorbance ratio approaches 1.27. This generates an Sao₂ reading of 75% to 80%, even though the maximum possible HbO₂ value is 35%. Therefore, the pulse oximeter progressively overestimates oxygen saturation with increasing methemoglobin concentrations and will not warn the clinician that a dangerous hypoxic state is developing.

These predictions were confirmed in our patients. In patient 1, as the methemoglobin concentration dropped from 54.8% to 15.2%, the HbO₂ level rose in proportion, but the Sao₂ values remained between 63% to 86% (Table 1). Pulse oximetry readings were greater than the HbO₂ levels until therapy decreased the methemoglobin concentrations to 5.6%. When methemoglobin concentrations are below 10% and the oxygen tensions are high, the remaining 90% of hemoglobin may be completely saturated with oxygen to give an HbO₂ value of 90%. This concentration of methemoglobin will cause an increase in the 660- to 940-nm ratio so that the Sao₂ reading is 91%, a fortuitous correlation with the HbO₂ level.^{10,11,16,17} However, if

the nonmethemoglobin fraction contains both HbO₂ and reduced hemoglobin, the SaO₂ values will be higher than the HbO₂ values.¹⁷

In both patients, the low SaO₂ readings in the presence of high PaO₂ values and calculated saturations suggested the presence of an abnormal type of hemoglobin. Transcutaneous oxygen monitoring provides values that reflect PaO₂ values and may be normal in the presence of severe methemoglobinemia.¹⁸ Oxygen saturation calculated from the arterial or transcutaneous oxygen tension values will provide a false sense of security, as these calculations are based on the assumption that all hemoglobin has the capacity to bind to oxygen. Since

methemoglobin has no oxygen-carrying capacity, the patient with methemoglobinemia is at risk for tissue hypoxia even if the PaO₂ value is high.^{9,10,12,16,18}

Methylene blue is known to have a dose-dependent artifactual effect on both HbO₂ and SaO₂ readings. This effect is transient and lasts for less than 30 minutes at the doses used in clinical practice.^{3,6} Since blood samples for cooximetry were drawn more than an hour after the administration of methylene blue in our patients, the differences between the low SaO₂ and HbO₂ readings cannot be explained by this artifactual effect.

A disparity between the oxygen saturation calculated from PaO₂ values and

pulse oximetry readings can be an important clue to the presence of methemoglobinemia. In these patients, pulse oximetry overestimates oxygen saturation and should not be used to reflect arterial oxygen content or tissue oxygen delivery. Therapy should be guided by direct measurements of HbO₂ and methemoglobin using a cooximeter and not on the basis of measurements using pulse oximetry or on estimates of calculated oxygen saturation.

We thank the nurses of the Pediatric Intensive Care Unit at St Louis Children's Hospital who provided the care for these patients. We also gratefully acknowledge the secretarial assistance of M. Bicknell.

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In Other AMA Journals

ARCHIVES OF OPHTHALMOLOGY

Controversies in Ocular Prophylaxis of Newborns

John W. Chandler, MD (*Arch Ophthalmol*. 1989;107:814-815)

Modification of an Ophthalmic Laser for Use in Sedated, Reclining Children

Lawrence M. Kaufman, MD, PhD (*Arch Ophthalmol*. 1989;107:928-929)

Toxic Shock Syndrome Caused by a Strain of *Staphylococcus aureus* That Produces Enterotoxin C but Not Toxic Shock Syndrome Toxin-1

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• An 8-month-old infant presented with pneumonia and pleural effusion associated with clinical manifestation of toxic shock syndrome. A *Staphylococcus aureus* strain isolated from the pleural fluid produced enterotoxin C, but not toxic shock syndrome toxin-1 or other enterotoxins. Acute and convalescent sera showed an antibody rise to enterotoxin C but not to toxic shock syndrome toxin-1. These findings support the possibility that enterotoxin C was the primary toxin associated with this infant's illness.

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Toxic shock syndrome (TSS) was first described in seven children by Todd et al¹ in 1978. Two years later, TSS was reported to occur primarily among healthy menstruating women, particularly those using high-absorbency tampons.^{2,3} A more recent update indicated that the syndrome occurs in men and nonmenstruating women, too, and that the proportion of nonmenstrual cases may be increasing.⁴

In 1981, a toxin responsible for TSS was identified independently by Schlievert et al⁵ and Bergdoll and colleagues.⁶ Called TSS toxin-1 (TSST-1), this toxin was produced by more than 90% of staphylococcal strains isolated from menstruating patients. In addition to TSST-1, enterotoxin B has primarily been associated with nonmenstrual TSS.^{4,7} Staphylococcal enterotoxin C was first isolated from an adult patient in whom

the two staphylococcal isolates produced enterotoxin C and TSST-1.⁸ Another report describes a "variant" TSS in a neonate born to a mother with TSS associated with enterotoxin C.⁹

Toxic shock syndrome is rare in infancy and there have been, to our knowledge, only two confirmed occurrences of TSS in children under 1 year of age.^{10,11} In this report we describe TSS in an 8-month-old child associated with *Staphylococcus aureus* producing enterotoxin C, but not TSST-1 or other enterotoxins.

REPORT OF A CASE

An 8-month-old boy was seen in the emergency department for respiratory distress and diarrhea. He was irritable, had a temperature of 41°C, a pulse rate of 195 beats per minute, and a respiratory rate of 60 to 80/min. He had conjunctival hyperemia with oral mucosal ulcerations, fissured lips, and excoriating diaper rash with scabbed lesions over the legs. Intercoastal and subcostal retractions were noted with decreased breath sounds over the right lung field.

Laboratory tests indicated a hemoglobin level of 110 g/L, a hematocrit of 0.33, and a white blood cell count of 9.5×10^6 /L with 0.43 polymorphonuclear leukocytes, 0.29 band forms, 0.22 lymphocytes, and 0.06 monocytes. Platelet count was 75×10^6 /L. Prothrombin time was 12 seconds, with control of 9 seconds; partial thromboplastin time was 51 seconds, with a control of 32 seconds. Fibrinogen level was 5.3 g/L. Blood urea nitrogen level was 6.5 mmol/L of urea with a creatinine level of 90 μ mol/L. Serum glutamic-pyruvic transaminase level was 88 IU/dL. Throat culture yielded normal flora. Cerebrospinal fluid and blood cultures were negative. There was no serologic evidence of leptospirosis. Chest roentgenogram showed a right lower lobe consolidation with pleural effusion.

Within 12 hours of admission, the patient

developed erythroderma of the palms, soles, perineum, and lips. The systolic blood pressure dropped to 64 mm Hg, requiring aggressive fluid replacement with Ringer's lactate solution (40 mL/kg of body weight), and plasmanate (20 mL/kg), in addition to dopamine hydrochloride.

After the pleural effusion was drained, parenteral treatment with nafcillin sodium and gentamicin sulfate was begun. Three days after admission, a fine desquamation of the skin was noted over the palms, soles, and perineum. There was no exfoliation of the skin in other areas nor was there any Nikolsky sign. The patient's respiratory status gradually improved, diarrhea subsided, and he was weaned off dopamine on the fifth hospital day, when his cardiovascular status stabilized. He received nafcillin for 21 days along with gentamicin for the first week. The patient was seen 10 weeks after hospital discharge and was doing well.

Staphylococcus aureus was isolated from the pleural effusion. When the organism was examined for toxin production, staphylococcal enterotoxin C was identified, but not TSST-1¹² or other enterotoxins. In addition, serologic tests demonstrated that the patient mounted an antibody response to enterotoxin C, with an acute serum antibody titer of 1:10 and convalescent titer (3 weeks later) of 1:320.¹³ In contrast, the serum titer against TSST-1 was 1:20 in both acute and convalescent samples.

COMMENT

Toxic shock syndrome is an acute multisystem disease characterized by high fever, hypotension, gastrointestinal symptoms, and an erythematous rash.^{1,3} The diagnosis of TSS in the patient described in this report was based on the clinical manifestations, which included a high fever and a diffuse erythematous rash associated with conjunctival hyperemia. Other pertinent signs included hypotension and evi-

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dence of disseminated intravascular coagulation. There was also evidence for involvement of the liver, gastrointestinal tract, lungs, and central nervous system. *Staphylococcus aureus* was isolated from the pleural fluid.

Although more than 90% of vaginal TSS *S aureus* strains produce TSST-1, only 50% to 60% of *S aureus* isolates obtained from other sites in cases of nonmenstrual TSS produce TSST-1.^{4,7} In addition, the production of staphylococcal enterotoxins by TSS-associated strains of *S aureus* is significantly increased over that of non-TSS strains, notably enterotoxin B.^{4,7} As illustrated by the patient described in this report, the *S aureus* isolated from the empyema fluid produced enterotoxin C but not TSST-1 or other enterotoxins. This enterotoxin has been shown to produce in primates many signs and symptoms similar to those observed in TSS in humans.¹⁴ The toxin shows a highly significant sequence homology with enterotoxin B.¹⁵

Green and LaPeter¹⁶ and Chow et al⁹ described two neonates with TSS resulting from possible intrapartum transmission. Chow et al⁹ have reported in 1984 a variant postpartum TSS with probable intrapartum transmission to the neonate due to *S aureus* producing enterotoxin C but not TSST-1. Toxic shock syndrome developed in both mother and infant despite preexisting high antibody titers to TSST and enterotoxin C. Nonmenstrual cases of TSS in children have been associated with skin infections after surgical procedures,¹⁰ abscesses,¹¹ tracheitis,¹⁷ empyema,¹⁸ adenitis,¹⁹ other or unknown sources of infection.¹⁰

The presence of *S aureus* producing TSS-associated toxins and the absence of antibody to the toxins in acute-phase sera have been considered as markers of

TSS.^{6,8} Elevated levels of anti-TSST-1 in acute-phase serum would be highly unlikely. So, in a patient with suspected TSS, in addition to examining the *S aureus* isolate for the ability to produce TSST-1 or enterotoxins, acute and convalescent sera should be tested for antibody against the toxins. Recent reports have described the association of TSS with *Staphylococcus hyicus* and with group A streptococcus.^{20,21} Of note is that the *S hyicus* elaborated TSST-1. Another study has shown that the group A streptococcal exotoxin possesses immunologic cross-reactivity with staphylococcal enterotoxin B and C1.²²

The patient described in this report is, to our knowledge, one of the youngest described as having TSS. The other unusual feature about this patient is that the *S aureus* isolated produced enterotoxin C but not TSST-1 or other enterotoxins. With the apparent increase in nonmenstrual patients with TSS, this disease should be suspected even in young children with sudden onset of fever, shock, diarrhea, rash, and evidence of multisystem illness associated with a staphylococcal infection.

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Alternating Sequential Dosing With Furosemide and Ethacrynic Acid in Drug Tolerance in the Newborn

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• Drug tolerance seems to develop rapidly after the administration of sequential doses of the same loop diuretic. We evaluated whether alternating different loop diuretics could achieve the same initial diuretic response in the newborn. In a randomized double crossover study, we examined the diuretic and saluretic effects of alternating doses of furosemide and ethacrynic acid (1 mg/kg administered intravenously every 24 hours) in 10 newborns, who received the drugs in the following sequential order: (1) furosemide, (2) ethacrynic acid, and (3) furosemide (group 1, $n=5$); and (1) ethacrynic acid (2) furosemide, and (3) ethacrynic acid (group 2, $n=5$). Hourly urine specimens were collected for the determination of rates of urinary and fractional excretion of sodium, chloride, and potassium and of urinary flow, before and 6 hours after dosing. There were no differences between the groups at each dose for all parameters measured. A significant decrease in pre-diuretic and postdiuretic rates of urinary flow, in sodium and chloride excretion, and in the fractional excretion of these electrolytes was observed before and after dosing. The associated reduction in patients' weights suggested a depletion in plasma volume. In conclusion, consecutive alternation of furosemide and ethacrynic acid in the same newborn does not prevent the development of pharmacologic tolerance to loop diuretics, since diuresis, natriuresis, and chloriuresis decrease after successive sequential administration of these drugs.

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Independent evaluations of furosemide and ethacrynic acid have shown that after administration of single doses, these drugs exert similar diuretic, natriuretic, and saluretic effects in the neonate.¹⁻⁶ However, during long-term administration of these agents, pharmacologic tolerance develops, resulting in a decrease in the diuretic response in both newborns and adults.^{6,7} This desensitization can be overcome in adults by substituting one loop diuretic for another, such as ethacrynic acid for furosemide.^{7,8} The reasons for the efficacy of this substitution may be attributed to differences in their mechanisms of action.⁹⁻¹¹ For instance, in addition to inhibiting renal tubular transport of chloride,⁷ furosemide, but not ethacrynic acid, can inhibit carbonic anhydrase,^{10,11} whereas only ethacrynic acid can inhibit $\text{Na}^+-\text{K}^+-\text{ATPase}$.⁹ To test whether the same initial response could be sustained by alternating furosemide and ethacrynic acid in the newborn, we examined the diuretic and saluretic effects after sequential administration in a randomized double crossover study.

PATIENTS AND METHODS

Patient Population

Newborns were entered in the study after informed consent by their legal guardians. This study was approved by the Sir Mortimer B. Davis Jewish General Hospital Ethics Committee, Montreal, Canada. Ten newborns with similar clinical demographic profiles (Table 1) were randomly assigned to two groups, as described below. The clinical status of the patients was the same in both groups at the time of the study. No patient presented any active medical problem, eg, ventilator or oxygen requirement, patent ductus arteriosus, or metabolic disturbance, during diuretic efficacy assessment. All patients were in a state of normal hydration,

which was maintained by the administration of well-established fluid requirements (130 to 150 mL/kg per day).¹² During the postnatal period (Table 1), major components of renal function, such as inulin clearance and natriuresis, are relatively stable.^{13,14} The newborns were weighed at the beginning of, and every 6 hours during, the study period. Fluid and electrolyte intake was unaltered after the newborns responded to the diuretics. None of the newborns received any concurrent drugs.

Diuretic Administration

The only indication for diuretic administration in all patients occurred after blood transfusion (7 mL/kg of packed red blood cells) for the correction of anemia resulting from iatrogenic blood loss.¹⁵ Administration of one or two doses of diuretics for blood transfusion is an accepted and common practice in our neonatal intensive care unit. The third dose of diuretic was administered for the purposes of the study, as approved by the hospital's ethics committee and after informed consent was given by the legal guardians of the patients. No patients had received diuretics for at least 1 week before entering

Table 1.—Clinical Variables

	Group (Mean \pm SD)*	
	1	2
Birth weight, g	1113 \pm 303	1159 \pm 379
Apgar score at 1 min	4.4 \pm 2.4	5.0 \pm 2.3
Apgar score at 5 min	7.2 \pm 1.3	7.2 \pm 1.6
Gestational age, wk	29.8 \pm 2.9	29.2 \pm 2.5
Postnatal age, d	38.4 \pm 10.5	55.2 \pm 18.6

*Diuretics (1 mg/kg per dose) were administered intravenously every 24 hours in the following order: group 1, (1) furosemide, (2) ethacrynic acid, and (3) furosemide; group 2, (1) ethacrynic acid, (2) furosemide, and (3) ethacrynic acid.

Table 2.—Rates of Urinary Flow, Electrolyte Excretion, Fractional Excretion of Electrolytes, and Creatinine Clearance*

Variable	Predose			Postdose		
	1st	2nd	3rd	1st	2nd	3rd
Flow Rates, mL/kg per Hour						
Urine						
Group 1	3.5 ± 0.7	1.7 ± 0.1†	2.4 ± 0.4†	7.4 ± 0.7	4.9 ± 1.0†	5.2 ± 1.8†
Group 2	3.1 ± 0.7	1.7 ± 0.4†	1.7 ± 0.4†	7.7 ± 1.2	5.0 ± 1.0†	5.4 ± 2.1†
Excretion Rates, μEq/kg per Hour						
Sodium						
Group 1	75 ± 24	27 ± 16†	22 ± 8†	626 ± 147	181 ± 134†	300 ± 186†
Group 2	63 ± 54	24 ± 13†	17 ± 10†	794 ± 191	298 ± 102†	389 ± 181†
Chloride						
Group 1	102 ± 29	43 ± 29†	23 ± 8†	808 ± 173	267 ± 189†	428 ± 190†
Group 2	81 ± 44	44 ± 28†	22 ± 9†	1015 ± 252	487 ± 107†	521 ± 237†
Potassium						
Group 1	137 ± 44	83 ± 31	90 ± 14	154 ± 14	149 ± 17	154 ± 20
Group 2	94 ± 38	71 ± 11	76 ± 10	184 ± 64	181 ± 39	219 ± 76
Fractional Excretions, %						
Sodium						
Group 1	0.6 ± 0.3	0.4 ± 0.1	0.1 ± 0.1†	7.5 ± 3.3	1.2 ± 1.1†	3.7 ± 1.8†
Group 2	1.7 ± 2.5	0.2 ± 0.1†	0.2 ± 0.1†	9.5 ± 4.1	1.6 ± 0.8†	2.9 ± 1.4†
Chloride						
Group 1	1.1 ± 0.6	0.8 ± 0.4	0.3 ± 0.1†	13 ± 5.6	2.6 ± 2.3†	7.8 ± 3.2†
Group 2	2.5 ± 3.3	0.5 ± 0.4	0.3 ± 0.1†	16 ± 6.1	3.8 ± 1.7†	6.3 ± 3.7†
Clearance, mL/min per 1.73 m²						
Creatinine						
Group 1	26 ± 12	29 ± 9	26 ± 11	21 ± 9	36 ± 18	30 ± 3
Group 2	20 ± 9	33 ± 5	30 ± 8	22 ± 7	32 ± 5	27 ± 9

*Values are mean ± SD. Diuretics were administered to each group in the following order: group 1, (1) furosemide, (2) ethacrynic acid, and (3) furosemide; group 2, (1) ethacrynic acid, (2) furosemide, and (3) ethacrynic acid.

† $P < .05$ vs the appropriate values before or after the first dose.

the study.

The 10 neonates were randomly assigned to begin receiving either furosemide or ethacrynic acid, after which the diuretics were alternated every 24 hours, for a total of three doses (1 mg/kg per dose administered intravenously). The time interval was chosen to minimize a carryover effect.^{1,3,6} Therefore, the two groups of newborns received the diuretics in the following sequential order: group 1 ($n = 5$), (1) furosemide, (2) ethacrynic acid, and (3) furosemide; group 2 ($n = 5$), (1) ethacrynic acid, (2) furosemide, and (3) ethacrynic acid.

Sample Collection and Measured Variables

Patients were placed on a metabolic bed installed in their isolettes, where urine was collected for the measurement of volume, electrolytes, and creatinine. The aliquots of urine were obtained 6 hours before (predose) and 6 hours after (postdose) the administration of each diuretic dose.^{1,3} Stools were collected separately and discarded.

Serum electrolyte, serum urea nitrogen, and creatinine concentrations were determined before administration of the first diuretic dose and 2 hours after each drug ad-

ministration. These measurements were obtained as part of the routine clinical care and, in part, for the purpose of this study, as approved by our hospital's ethics committee and consented to by the patients' legal guardians.

The above measurements, obtained before and after the administration of each drug dose, were used to calculate urinary flow rates (expressed in milliliters per kilogram per hour); fractional excretions of sodium and of chloride (expressed as a percent of the creatinine clearance); sodium, chloride, and potassium excretion rates (expressed in microequivalents per kilogram per hour); and creatinine clearance (expressed in milliliters per minute per 1.73 m²). Osmolar clearance was not included because of the limited volume of the blood samples.

Statistical Analysis

Data analyses were performed using paired and unpaired Student's *t* tests, one-way ANOVA for repeated measurements, the Mann-Whitney *U* Test, and the Wilcoxon Rank-Sum Test. Due to sample size, non-parametric tests were also performed; the latter confirmed analysis obtained from the parametric tests. The results are expressed

as mean ± SD. Statistical significance was set at $P < .05$.

RESULTS

Pharmacologic Effects of Sequentially Alternating Furosemide and Ethacrynic Acid

The rates of urinary flow, electrolyte excretion, fractional electrolyte excretion, and creatinine clearance, for the 6 hours after administration of the bolus, are presented in Table 2. No differences in rates of urinary flow, excretion or fractional excretion of electrolytes (Table 2, postdose results), or creatinine clearance were found at each dose between groups 1 and 2.

Compared with the effects after the first dose, a decrease in urinary flow was demonstrated in all patients in groups 1 and 2 after the second and third diuretic doses (group 1, $P < .03$; group 2, $P < .04$; Fig 1 and Table 2, postdose values). Sodium and chloride urinary excretion rates ($P < .01$), and the urinary fractional excretion rates of these elec-

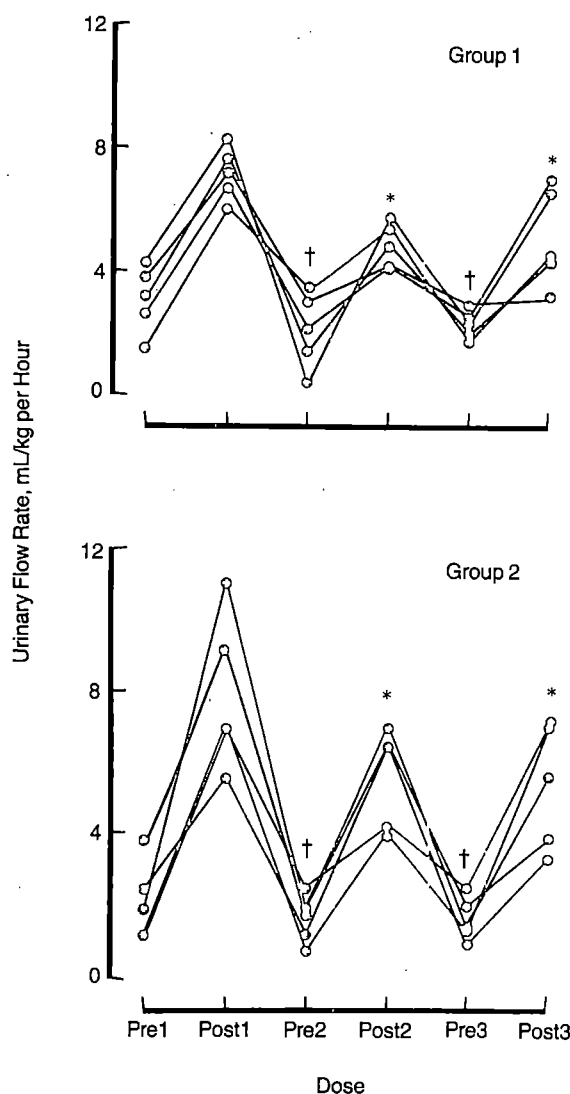


Fig 1.—Urinary flow rate as a function of diuretic dose sequence in each patient. Diuretics (1 mg/kg per dose) were administered intravenously every 24 hours in the following order: group 1, (1) furosemide, (2) ethacrynic acid, and (3) furosemide; group 2, (1) ethacrynic acid, (2) furosemide, and (3) ethacrynic acid. The numbers 1, 2, and 3 on the abscissa refer to the dose order (eg, pre1 indicates before the first dose; post1, after the first dose). The asterisk indicates $P < .05$ vs post1 (Wilcoxon Rank-Sum Test); dagger, $P < .05$ vs pre1 (Wilcoxon Rank-Sum Test).

trolytes ($P < .005$), were also shown to decrease in both groups (Table 2, post-dose values). Potassium excretion rates and urinary creatinine clearance rates did not change in either group of patients. Very similar findings were obtained when responses in the rates of urinary flow, electrolyte excretion, and

fractional excretion of electrolytes for each patient were analyzed as *percent changes from respective predose values*.

To evaluate whether these decreases in diuretic, natriuretic, and chloriuretic responses resulted from a possible decrease in plasma volume, secondary to the diuretic action, we analyzed the *pre-*

diuretic rates of urinary flow, sodium and chloride excretion, and fractional sodium and chloride excretion in both groups. A gradual reduction in these parameters was observed in both groups ($P < .05$; Fig 1 and Table 2, predose values). In addition, there was a slight but significant decrease in the weights of the infants at the end of the experiment. The respective weights before the first dose and after the last dose were as follows: group 1, 1958 ± 116 g and 1851 ± 127 g ($P < .05$); group 2, 2149 ± 137 g and 2064 ± 118 g ($P < .05$). This reduction in rates of *prediuretic* urinary flow, urinary fractional excretion, and sodium and chloride excretion after the first drug dose suggested a diminished plasma volume.

Serum electrolyte, serum urea nitrogen, and creatinine concentrations remained stable throughout the study, except for a slight decrease in chloride concentration in group 2, from 108.0 ± 0.7 mEq/L to 101.8 ± 2.9 mEq/L ($P < .01$), before the first dose and after the third dose, respectively. Rates of urinary flow, electrolyte excretion, and fractional electrolyte excretion did not correlate with birth weight or with gestational, postnatal, or postconceptional age, as previously observed.^{1,3}

Relationship Between the Pharmacodynamic Effects of Furosemide and Ethacrynic Acid, and Correlation of the Effect of the Initial Dose of One Drug With Its Second Dose

Since it is well recognized that there is a great deal of interpatient variability involved in the use of diuretics,^{1-3,7} we assessed whether, in the same patient, the response to the first dose of either drug correlated to that of the second drug (second dose). The groups were combined, since they were very similar in their responses to the diuretics, as previously shown. A significant correlation was only found for the rate of urinary flow ($r = .81$; $P < .01$; Fig 2, second dose vs first dose). When the responses were analyzed as percent changes from baseline, there was again a significant correlation in the rate of urinary flow between the first and second doses ($r = .65$; $P < .01$). These findings suggest that subjects with the greatest diuretic response to the first drug maintained an

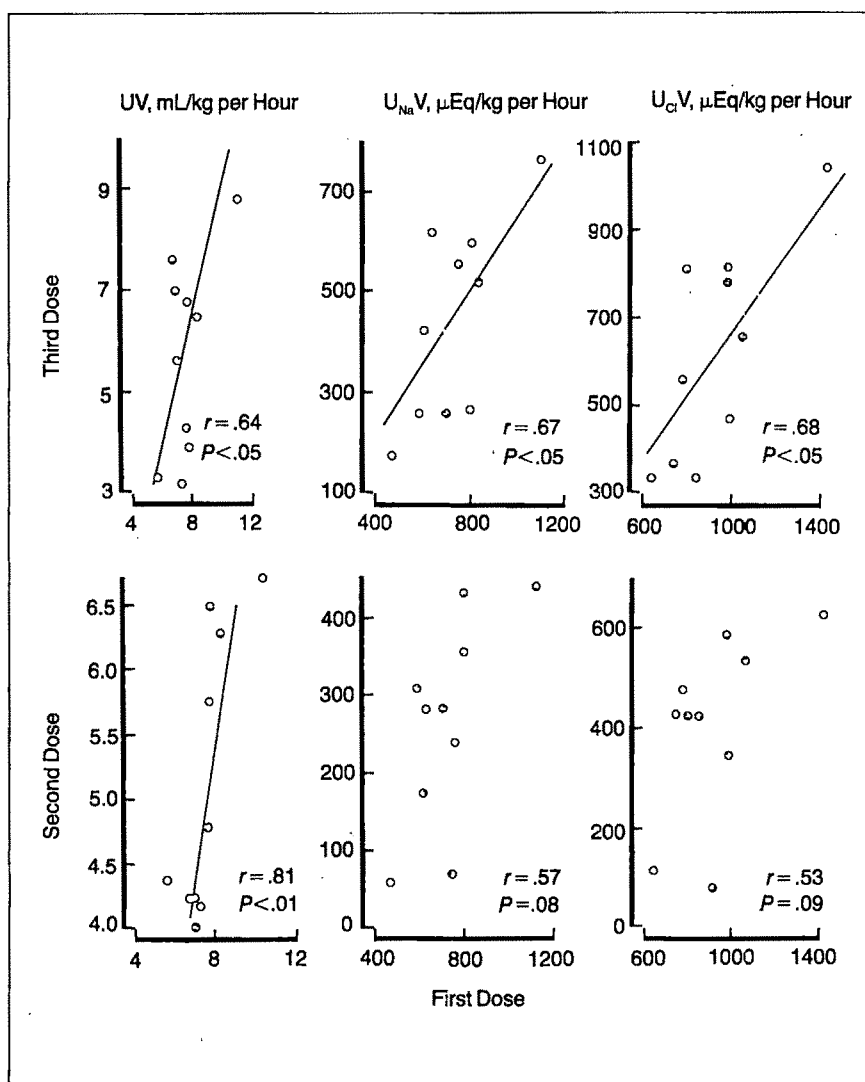


Fig 2.—Relationship of the urinary flow rate (UV) and sodium ($U_{Na}V$) and chloride ($U_{Cl}V$) excretion rates between furosemide and ethacrynic acid (second dose vs first dose, bottom graphs) and between the first and third (ie, the second dose of the first diuretic administered) diuretic doses (top graphs). Regression line is indicated only where a significant relationship ($P < .05$) exists.

enhanced response to the second drug. Similarly, patients with the lowest diuretic response to the first agent continued to respond the least to the second agent. Therefore, the magnitude of response is maintained in the same patient.

We also assessed whether the response to a drug is maintained after its second administration, ie, the third dose. As shown in Fig 2 (third dose vs first dose), a significant correlation was found for rates of urinary flow ($r = .64$) and sodium ($r = .67$), chloride ($r = .68$), and potassium ($r = .84$; latter not shown) excretion ($P < .05$). These corre-

lations were also observed when responses were analyzed on the basis of percent change. Thus, the subject's qualitative response to the same agent is maintained; patients with the greatest response maintained the same high response, and those with the lowest response continued to respond the least to the same drug.

COMMENT

The aim of this study was to determine whether the development of pharmacologic tolerance to a single diuretic administered over an extended period^{6,7} can be avoided by alternating consecu-

tive doses of furosemide and ethacrynic acid in the newborn. Our data show that despite the alternation of furosemide and ethacrynic acid during consecutive drug doses, there is a decrease in diuresis, natriuresis, and chlориuresis after the initial dose of either of these diuretics. The results are comparable with those observed in two studies of the long-term administration of furosemide in newborns and adults.^{6,7} These studies showed that there is a decrease in the pharmacodynamic response to the second and subsequent doses of furosemide relative to the response to the first dose. However, in contrast to findings in the adult, in whom the substitution of ethacrynic acid for furosemide reestablished the response,^{7,8} this result was not observed in the newborn.

Many studies have already shown that tolerance develops after the administration of consecutive doses of loop diuretics in both the newborn and the adult.^{6,7,16} We therefore did not think that it was ethically justified to replicate these studies and to subject our patients to parallel experiments using the same agent repeatedly, to enable within-study comparison. From a clinical point of view, our results had clearly demonstrated that switching loop diuretics in the newborn failed to avoid the rapidly developing pharmacologic tolerance to a single drug. If tolerance may partly result from a reduction in plasma volume,^{6,7,16} it is possible that other patient populations with fluid overload states, such as infants with bronchopulmonary dysplasia, may not respond more favorably to alternate sequential doses of furosemide and ethacrynic acid.⁶

The possible mechanisms of this tolerance to consecutive doses of loop diuretics were not examined in this study, and remain to be explored. However, certain inferences may be speculated from our data. We have observed a decrease in *prediuretic* rates of urinary flow, fractional excretion, and excretion of sodium and chloride (Fig 1 and Table 2, predose values). These decreases, which were associated with the decrease in patients' weights, were suggestive of a diminished plasma volume, possibly contributing to this rapid development of tolerance, as previously proposed in the adult.^{7,16} Although prediuretic creatinine clearance had not de-

creased after the first dose of either drug, this parameter of measure of glomerular filtration rate has limitations in the newborn,^{17,18} in contrast to the more accurate but more invasive inulin clearance.^{18,19} Furthermore, mild volume depletion, initially not associated with changes in glomerular filtration, leads to increased proximal tubular reabsorption of fluid.²⁰ Consequently, regardless of the glomerular filtration rate, proximal tubular reabsorption may be enhanced; therefore, less sodium and chloride are delivered to the site of action of the loop diuretics.⁷

Recent findings indicate that decreased extracellular fluid volume seems to be the cause of tolerance to loop diuretics.^{7,16} Reversal of this tolerance by the substitution of loop diuretics in the adult⁷ may result from their effects at different sites of action.⁸ In contrast, tolerance to diuretics in the newborn, despite the alternation of consecutive doses of these agents, persists, perhaps because in younger subjects there is a relative lack of efficacy of diuretics on other sites of action, com-

pared with their principal one. This, however, needs to be evaluated.

The significant correlations in diuresis found between repetitive doses of the same drug (first dose vs third dose) and between the two different drugs (first dose vs second dose) imply that the magnitude of response is maintained in the same subject. Hence, newborns with better responses or those with lower responses preserve their ability to respond, regardless of the agent subsequently administered. The findings are consistent with each individual's physiologic capability to balance sodium concentration and fluid volume.⁷ These data imply that the continued administration of loop diuretics in an infant who is not adequately responding to the first dose may not achieve therapeutic objectives but may accumulate and produce toxicity.²¹ We have found a consistent, although statistically nonsignificant, increase in urinary electrolyte excretion and fractional excretion of sodium and chloride after the third diuretic dose, without further changes in urinary output (Table 2,

postdose results). In addition, a concomitant decrease in serum chloride concentration was observed. These findings are in accord with the clinical observation that chronic dosing can lead to adverse effects by causing ongoing losses of electrolytes despite a reduced urinary output.

In conclusion, alternating sequential administration of furosemide and ethacrynic acid in the newborn infant does not prevent the development of pharmacologic tolerance to these drugs. Future investigations using combined diuretics that clearly act at separate tubular sites may reveal advantages to this type of therapy.²² Such pharmacologic approaches may improve therapeutic response in patients who require long-term diuretic treatment, such as preterm infants with bronchopulmonary dysplasia.

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Prescription of Psychotropics to Children in Office-Based Practice

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• Multiple authors have stressed the need for close follow-up and simultaneous psychotherapy in most children treated with psychotropic drugs. However, little is known about the actual prescription of psychotropic medications in pediatric settings. Using the 1985 National Ambulatory Medical Care Survey, we investigated the frequency of follow-up arrangements and concurrent psychotherapy among US children in visits to office-based practices. We then explored determinants of psychotropic drug prescriptions. Mental health indicators, sociodemographic characteristics, provider type, and provider familiarity with the patient were important predictors of psychotropic prescriptions. Few providers report referral or concurrent psychotherapy for their patients receiving psychotropics, and follow-up plans were no different for children with or without psychotropics after controlling for other variables. This means that many children in outpatient care who are taking psychotropic medications may not be receiving optimal management for behavioral or emotional problems.

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Psychotropic drug prescription patterns are "an extremely important issue in health and social policy"¹ research because of these drugs' relatively high cost, frequent potential for addiction or habituation, possible interactions with other drugs, and serious implications for the long-term growth and

cognition of children.²⁻⁴ Numerous articles have recently reviewed and revised the indications for psychotropic drug use in the management of outpatient pediatric mental disorders and symptoms.^{2,4,6} These studies suggest the need for frequent follow-up of children receiving psychotropic medications and the importance of simultaneous psychotherapy in the majority of pediatric behavioral and emotional disorders. However, little is known about the actual prescription of psychotropic medications in pediatric health care settings.

National and community studies on the prescription of drugs in ambulatory pediatric settings have focused primarily on the most frequent medications and classes of medications prescribed, usually antibiotics.^{7,8} These studies have not discussed the frequency of use or factors associated with the use of psychotropic drugs.

Studies that do focus on psychotropic drug prescriptions have used surveys of students and teachers, not physicians, to identify the frequency of psychotropic medication use among US children.⁹⁻¹¹ These studies have usually discussed stimulant medications for hyperactivity and attention-deficit disorder.

Little information has been published on prescription practices for this class of drugs in ambulatory pediatric care in the United States by psychiatrists or primary care providers. The few studies of children treated with psychotropics report that stimulants are the predominant form of pharmacologic therapy in school-based populations^{5,11} and that psychotropics may be underutilized in children referred for mental health problems.¹² Unfortunately, these findings are limited by small sample sizes, recall problems and potential sampling bias. In addition, they do not address

concurrent psychotherapy or follow-up planning by physicians for children receiving psychotropic drugs. We believe it is important to know what psychotropic drugs physicians are prescribing and how they are treating these children.

Using the 1985 National Ambulatory Medical Care Survey (NAMCS), a national probability survey of patient visits to office-based practices, we summarize the prescription of psychotropic drugs to children and adolescents in the United States by patient and provider characteristics. Among children receiving psychotropic or stimulant prescriptions, we assess the following: (1) frequency of follow-up arrangements, (2) frequency of concurrent psychotherapy, and (3) characteristics of patients and providers as reported by psychiatrists and primary care physicians. Finally, we explore the determinants of psychotropic drug prescriptions during office-based visits for ambulatory medical care. We hypothesize that mental health indicators, sociodemographic factors, and type of health care provider will be important determinants of psychotropic drug prescriptions in office-based practice.

METHODS

Sample and Analysis Strategy

The 1985 NAMCS is a national sample of patient records from office-based physicians engaged in patient care activities, as defined by the American Medical Association and American Osteopathic Association.¹³ The data were collected by the National Center for Health Statistics (NCHS) and include 71 594 records of patient visits to 2879 physicians from a sample of 4104 physicians, a response rate of 70.2%; 12 320 visits were by patients less than 18 years of age. There was a national estimated total of 138 255 812 visits by patients less than 18 years of age in 1985. For this analysis, all children who had missing drug prescription data ($n=186$) were eliminated.

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The NCHS used a multistage probability design for the 1985 NAMCS: Counties or Standard Metropolitan Statistical Areas were stratified by size, region, and demographic characteristics. Physicians within areas were stratified by specialty. Physicians were selected by an NCHS allocation formula (details are available from the NCHS). Finally, patient visits were randomly selected from all visits to selected physicians in one randomly chosen week of the year. Actual data collection was performed by the physician, aided by office staff.

Because selection was not completely random and because the NCHS wanted to be able to provide national estimates of office visits, the NCHS assigned each visit a weight. The weight corrects for the design effect of a stratified complex sample so that the sample population may be used to estimate the total number of national visits to office-based practices and to estimate appropriate SDs for the sample. The base population used to compute annual visit rates is derived from estimates by the US Bureau of the Census of the civilian, noninstitutionalized population as of July 1, 1985. Because of the design effect, it is important to report both the actual number of pediatric visits as well as the nationally based weighted percentage. Standard deviations and confidence intervals are based on the weighted proportions. For differences between proportions, SEs were estimated, confidence intervals were constructed for each proportion, and a determination was made as to whether the intervals (95% or 99%) overlapped. Children who were prescribed at least one psychotropic medication were compared with children not receiving psychotropics on sociodemographic factors, provider type, familiarity with the provider, psychiatric recognition factors, and follow-up plans. Subsequently, children receiving stimulant medications were compared with children not receiving psychotropics by use of the same variables.

To determine the factors associated with receipt of psychotropic medication during a pediatric visit, a logistic regression model was estimated. A logistic regression analysis was performed for two reasons: (1) The effects of each variable can be examined independently. (2) An analysis of group differences using confidence intervals is extremely conservative. Logistic regression provides single-degree-of-freedom tests for trend that are more powerful than tests of the null hypothesis in bivariate analyses.¹⁴

The statistic presented in a logistic regression is the odds ratio. An odds ratio greater than 1 signifies a greater-than-average risk of receiving a psychotropic prescription. An odds ratio less than 1 signifies a below-average risk. An odds ratio equal to 1 signifies average risk and is considered not sig-

nificant.

Since the exact NCHS sampling probabilities are not published, multivariate analyses of these data cannot take advantage of the computer programs used to adjust for non-random sampling. However, to ignore the weights in the analysis would underestimate the SE estimates, and to use the weights would inflate the sample size into the millions, making all variables significant. Therefore, following the method of Lee et al,¹⁵ each weight was divided by the average weight for the total sample. Thus, the original pediatric sample size and the NCHS weights were retained. The most statistically parsimonious model is presented in the results (ie, the model contains only significant odds ratios or those significantly >1).

Measures

Mental Health Indicators.—The three indicators used to designate a mental health visit were psychiatric reason for visit, psychiatric diagnosis, and psychotherapy. Psychotropic drug prescription was not included as an indicator of a visit for mental health purposes since it was the dependent variable of interest.

The dependent variable was prescription of psychotropic drugs in ambulatory care. Prescription refers to the ordering or providing of a psychotropic drug by a physician and does not take into account patient compliance with physician instruction. Psychotropic drugs are the agents named by physicians in the 1985 NAMCS that had been designated as psychotropic by the NCHS and subdivided into anti-anxiety, antidepressant, and anti-psychotic agents. A further category, stimulants, was added for this study of children. Physicians were instructed to report both new and continued medications in the survey.

Because some patients received psychotropic drugs for physical conditions not related to mental health problems, the NCHS developed a list of non-mental health diagnoses for which psychotropic drugs are indicated in adult populations. Certain diagnoses germane to pediatric practice were added to that list (eg, vomiting and phenothiazines, primary enuresis and tricyclics, leukemia and phenothiazines, and epilepsy and barbiturates), and any visits for these conditions were excluded from further analyses, although these cases accounted for only a few visits.

Reasons for visit were recorded by physicians using the NCHS Reasons for Visit Classification Tabular List. Psychiatric reasons for visits include mental disorders, symptoms referable to psychological and mental disorders, psychiatric examinations, psychotherapy or counseling, and some symptoms referable to the nervous system.

Diagnoses were coded by physicians using the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*.¹⁶ Psychiatric diagnoses used in this study include ICD-9-CM 290.00 through 319.00.

On the NCHS form, physicians were specifically asked whether a visit included psychotherapy or counseling. This question was used as the indicator of whether psychotherapy was provided.

The disposition of visit was also listed as a separate question, with planned visits or telephone calls considered "scheduled follow-up," while no planned follow-up and return visits as needed were considered "no follow-up planned." Referrals and admissions to hospitals or other dispositions were considered separately.

Sociodemographic Factors.—Age was coded into four levels of 0 to 3, 4 to 8, 9 to 13, and 14 to 17 years. These divisions reflect various developmental stages during which changes in behavior and emotional disorders can be expected, and, therefore, might have an impact on physician prescribing practices.

Race and gender were also included in the regression model because prescribing patterns vary by gender, and race has been associated with differential receipt of other health services. The primary source of payment as recorded was also compared, for the same reasons. All of the above were specific questions on the NAMCS form. Finally, because prescription of psychotropic drugs is frequently inappropriate on a first visit in an office-based setting, patient status (returning patient vs new patient) and the payment method for visits were included.

Provider Type.—Physician specialty was collapsed into five categories: (1) pediatrics, (2) psychiatry (child and other), (3) primary care (family practitioners and general practice), (4) internal medicine, and (5) other (including pediatric subspecialists).

RESULTS

In this study of pediatric visits to physicians in ambulatory medical care settings, 1.5% of the visits by children included the prescription of a psychotropic drug that met the study criteria. The physicians prescribing those drugs had widely divergent prescription patterns. Table 1 shows rates of psychotropic prescriptions per 100 000 visits based on NCHS estimates from the US Bureau of the Census from 1985. Psychiatrists more frequently prescribed a psychotropic drug during a visit than physicians in any of the other medical specialties and are the primary prescribers of stimulants, although the rate

Table 1.—Rates of Prescription of Psychotropic Drugs to Children

Prescribing Physician	No. of Visits	Prescription Rate (per 100 000 Visits) by Drug Type*			
		Anxiolytic	Antidepressant	Antipsychotic	Stimulant
General or family practitioner	3237	730	50	90	120
Pediatrician	4513	310	50	30	140
Internist	250	500	3280	400	90
Psychiatrist	204	1300	6520	7050	10750
All others	4116	750	190	110	130

*These rates are based on the proportion of pediatric visits (weighted to the national estimates of yearly visits) to each provider during which a psychotropic drug of the type specified was given.

Table 2.—Demographic Characteristics of Children in Office-Based Ambulatory Settings

	No Psychotropic Drug, No. (Weighted %)* of Children	Any Psychotropic Drug, No. (Weighted %)* of Children	Stimulant, No. (Weighted %)* of Children
Age, y			
0-3†	4649 (43.0)	30 (14.7)	0
4-8	2793 (22.5)	56 (27.5)	26 (53.3)
9-12	1665 (13.0)	35 (19.5)	11 (28.4)
13-17‡	3027 (21.5)	65 (38.3)	9 (18.3)
Sex			
F	5916 (50.1)	81 (39.0)	10 (20.8)
M	6218 (49.9)	105 (61.0)	36 (79.2)
Race			
Nonwhite	1283 (10.7)	23 (13.1)	9 (20.7)
White	10851 (89.3)	163 (86.9)	37 (79.3)
Insurance§			
Medicare/Medicaid	1402 (10.4)	30 (14.2)	5 (10.4)
Blue Cross or commercial	3514 (26.4)	68 (30.9)	22 (41.8)
Health maintenance organization	1212 (11.2)	16 (6.8)	4 (6.4)
Self	6505 (55.6)	83 (48.5)	18 (43.4)

*According to the National Center for Health Statistics, only weighted percentages are to be presented. The weights correct for the nonrandom sample design and inflate the sample to an estimate of the total number of ambulatory visits made in 1985.

† $P < .01$ for no psychotropic drug compared with any psychotropic drug.

‡ $P < .05$ for no psychotropic drug compared with stimulant.

§Insurance percentages do not add to 100% because more than one choice was possible.

for psychiatrists is based on a small number of actual visits ($n = 204$). However, even among those physicians who can be considered primary care physicians (pediatricians, general and family practitioners, and internists), for whom presenting symptoms and diagnoses could be similar, there are marked differences in prescribing patterns. Pediatricians are the least likely to prescribe psychotropics and internists the most likely. Pediatricians and general and family practitioners are more likely to prescribe anxiolytics than any other psychotropic agent, and internists more frequently prescribed antidepressants.

Table 2 presents the demographic

characteristics by drug prescription status of the patients making pediatric visits. Only the age of the patient is significantly associated with whether a psychotropic prescription was given. Children 0 to 3 years of age were significantly less likely to receive a psychotropic prescription than other children, and children 13 to 17 years old were significantly more likely to receive a prescription.

Because of the small number of children receiving stimulants, tests of significance showed no difference between children receiving stimulants and those who received no psychotropic drugs. However, 4- to 8-year-old children and

boys more frequently received stimulants during office visits. Children 0 to 3 years old received no stimulants in this sample.

Table 3 presents the clinical characteristics of the children. Children who received psychotropic drugs and those who received a prescription for stimulants had been seen previously for the same problem significantly more often. New patients or returning patients with new problems were much less likely to receive psychotropic drug prescriptions.

Recognition of a psychiatric condition and physician management plans were powerful predictors of prescription of psychotropic drugs. A psychiatric diagnosis and the reason for visit both predicted receipt of psychotropics of any type. Children who received some type of psychiatric counseling were also more likely to receive psychotropic drugs. Before controlling for other variables, physicians who gave psychotropic prescriptions were more likely to have specified some plan of follow-up with the child. The children who did not receive a prescription were more likely than those who did to have been given no specific follow-up plan.

In Table 4, psychiatric diagnoses, psychotherapy, and follow-up among children receiving psychotropic drugs are presented. Approximately one fifth of children who were prescribed psychotropics received psychotherapy, follow-up, and a psychiatric diagnosis in their visit. One third received either psychotherapy and follow-up plans or a specific psychiatric diagnosis and follow-up plans in addition to psychotropic prescriptions.

The logistic regression model in Table 5 presents the most statistically powerful variables predicting prescription of psychotropic drugs to children in ambulatory medical care settings. Adjusting for all significant factors, the children who are most likely to receive a psychotropic drug prescription are those who are given a psychiatric diagnosis, present with a psychiatric reason for visit, are boys, or are returning to the physician with a previous complaint. Children least likely to receive a psychotropic prescription are those under the age of 9 years and those seeking care from a pediatrician.

Table 3.—Clinical Characteristics of Children in Office-Based Ambulatory Settings

	No Psychotropic Drug, No. (Weighted %)* of Children	Any Psychotropic Drug, No. (Weighted %)* of Children	Stimulant, No. (Weighted %)* of Children
Provider			
Internal medicine	244 (2.4)	6 (9.2)	1 (1.0)
Primary care	3198 (26.8)	39 (25.5)	7 (14.8)
Pediatrics†	4474 (49.0)	39 (23.6)	9 (30.1)
Psychiatry†	159 (0.7)	45 (18.6)	21 (41.8)
Other	4059 (21.1)	57 (23.1)	8 (12.3)
Visit status			
New patient‡	2643 (18.6)	19 (9.3)	2 (6.1)
Return patient, old problem§	5918 (46.9)	132 (71.7)	41 (85.3)
Return patient, new problem‡§	3573 (34.6)	35 (19.0)	3 (8.6)
Psychiatric recognition factors			
Diagnosis†§	228 (1.2)	82 (40.1)	39 (85.0)
Reason for visit†§	243 (1.5)	66 (36.7)	32 (69.6)
ICD-9-CM V-code	14 (0.1)	1 (0.9)	0
Psychotherapy or counseling†¶	1215 (9.6)	66 (36.2)	26 (48.7)
Management#			
Planned return†§	6709 (53.3)	137 (72.2)	39 (88.4)
As needed or none†§	5252 (46.3)	50 (26.4)	6 (9.9)
Referred	260 (2.2)	3 (4.2)	1 (1.7)
Other	267 (1.7)	1 (0.8)	0

*According to the National Center for Health Statistics, only weighted percentages are to be presented. The weights correct for the nonrandom sample design and inflate the sample to an estimate of the total number of ambulatory visits made in 1985.

† $P < .01$ for no psychotropic drug compared with any psychotropic drug.

‡ $P < .05$ for no psychotropic drug compared with any psychotropic drug.

§ $P < .01$ for no psychotropic drug compared with stimulant.

||ICD-9-CM indicates the *International Classification of Diseases, Ninth Revision, Clinical Modification*.

¶ $P < .05$ for no psychotropic drug compared with stimulant.

#Management percentages do not add to 100% because more than one choice was possible.

COMMENT

To our knowledge, this is the first national study of psychotropic drug prescriptions in outpatient settings for children. In our study, psychotropics were infrequently prescribed during all primary and specialty care outpatient visits by children. Although psychotropic agents were not often prescribed, we found patient characteristics, mental health indicators, and type of provider to be important predictors of psychotropic drug prescriptions in office-based visits by children. The data also suggest that children who receive psychotropic drug prescriptions may be receiving inadequate follow-up care and are not usually receiving concurrent psychotherapy.

Considerable clinical deviation exists between these findings and standards of

care recommended for children treated with psychotropic drugs,^{16,17} which include close follow-up and simultaneous psychotherapy. Controlling for all statistically significant factors in our analyses, children who were prescribed psychotropic drugs were no more likely to have follow-up than children not receiving psychotropics. Over 26% of the children receiving psychotropic medications were not scheduled for follow-up visits. Possible explanations for the lack of scheduled follow-up among many children for whom psychotropics were prescribed include a reliance by some providers on long-term relationships with families expected to report side effects, failure to record accurately the follow-up status on the survey form, or a failure to appreciate the serious implications and side effects of these drugs. Elucidation of these mechanisms will

Table 4.—Psychiatric Diagnosis, Follow-up, and Counseling of Children Receiving Psychotropic Drug Prescriptions

Management	No. (Weighted %)* of Children
Psychiatric diagnosis	82 (40.1)
Follow-up appointment	137 (72.2)
Psychotherapy or counseling	66 (36.2)
Diagnosis and follow-up	69 (34.3)
Diagnosis and counseling	48 (23.5)
Counseling and follow-up	59 (33.3)
Diagnosis, follow-up, and counseling	43 (21.5)

*According to the National Center for Health Statistics, only weighted percentages are to be presented. The weights correct for the nonrandom sample design and inflate the sample to an estimate of the total number of ambulatory visits made in 1985.

require provider-specific research.

Besides failing to specify follow-up for many children treated with psychotropic drugs, providers usually did not report psychotherapy for these patients. Although receipt of psychotherapy was associated with psychotropic drug prescriptions, only 36.2% of children given psychotropic medications were provided counseling or psychotherapy during office visits. Less than 22% of children who were prescribed psychotropic drugs in office-based settings received a psychiatric diagnosis, planned follow-up, and counseling or psychotherapy during their ambulatory visit according to providers. Referrals were also rare for children receiving psychotropic drugs in outpatient settings during these visits. Lack of concurrent psychotherapy and insufficient follow-up suggest that many children given psychotropic drugs in outpatient settings are receiving less-than-optimal management.

Because the 1985 NAMCS data are visit-based instead of patient-based and the appropriateness of diagnosis and management by providers cannot be assessed directly, our findings concerning follow-up and concurrent psychotherapy by providers should be interpreted with caution. This is even more important in evaluating rates of psychotropic prescriptions that are uncorrected for confounding factors and severity of illness. Findings on particular subspecial-

Table 5.—Logistic Regression Predicting Prescription of Psychotropic Drugs

	Odds Ratio* (95% Confidence Interval)	P
Psychiatric diagnosis	13.53 (6.44-28.45)	.0000
Psychiatric reason for visit	3.52 (1.63-7.57)	.001
Male	1.46 (1.00-2.14)	.05
Age 0 to 3 y	0.43 (0.25-0.73)	.002
Return patient, same problem	2.11 (1.40-3.17)	.0004
Physician consulted pediatrician	0.61 (0.39-0.95)	.03

*Odds ratios greater than 1 indicate that an individual with a given characteristic (controlling for all other characteristics in the model) has a greater than 50% chance of receiving a psychotropic drug. Odds ratios less than 1 indicate that an individual with a given characteristic has a less than 50% chance of receiving a psychotropic drug. Odds ratios of 1 were eliminated from the model since they show no increased or decreased risk of receiving a prescription for a psychotropic drug (the characteristic does not predict receipt of a prescription).

ties are especially suspect because of the small sample size. Therefore, the estimates of visits per 100 000 population for some subspecialties are likely to be unstable. Another potential source of error is the inability of the NAMCS to account for telephone and renewal prescriptions for psychotropics that are likely to be made without close follow-up or concurrent behavioral counseling. These prescribing behaviors would increase the significance of our findings. On the other hand, ongoing psychotherapy that is known about but not mentioned by the provider is another possible source of error. Additional psychotherapy would decrease the significance of our findings. Multiple psy-

chotropic prescriptions to one child did not affect findings for the regression equation, since all children with at least one psychotropic prescription were considered. However, multiple prescriptions to one child in a visit may have affected the uncorrected estimates of psychotropic prescription rates per 100 000 visits for some specialties with few visits.

Future research to clarify these findings would benefit from a longitudinal design and standardized psychiatric diagnoses. Ideally, provider treatment practices should be studied on a diagnosis-specific basis,¹⁸ using reliable instruments to assess the physical and mental health status of patients. Furthermore,

we recognize the insufficiency of one or several researchers deciding on best-care approaches. Instead, standards of care should be established for prescriptions of psychotropic drugs in pediatric ambulatory care similar to standards of care available now for adult psychiatric patients.¹⁹

In conclusion, we found that mental health indicators, sociodemographic characteristics, provider type, and provider familiarity with the patient were important factors in predicting receipt of psychotropic drugs during ambulatory visits. In addition, few providers report referral or concurrent psychotherapy for their pediatric patients receiving psychotropic medications. After controlling for other variables, follow-up plans were no different for children receiving psychotropics than for those not receiving psychotropic medications. Scheduled follow-up visits and combined treatment approaches using behavioral or cognitive therapy in combination with psychotropic drugs, when indicated, have been repeatedly recommended in the literature for the ambulatory management of most pediatric psychosocial problems. This means that many children in outpatient care taking psychotropic medications may not be receiving optimal management for behavioral or emotional problems.

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Normative Oscillometric Blood Pressure Values in the First 5 Years in an Office Setting

Myung K. Park, MD, Shirley M. Menard, RN, MSN

• We measured blood pressure (BP) and heart rate in 1554 healthy infants and children aged 2 weeks to 5 years using an oscillometric device, to establish normative values in this age group. The BP cuff width was selected to be 40% to 50% of the circumference of the upper arm. Triplicate measurements of BP and heart rate were obtained in the waiting room of pediatricians' offices and well-baby clinics before the patients were examined by the physician or nurse. Three readings were possible in 87% of the infants less than 3 years of age and in all children 3 years of age and older. The average BP value (systolic/diastolic [mean]) increased rapidly from the 2- to 3-week value of 78/47 (59) mm Hg to the 1- to 5-month value of 95/60 (74) mm Hg. No subsequent increase in BP occurred until 2 years of age (96/56 [71] mm Hg) when systolic and mean pressures started to increase at an average annual rate of 2 mm Hg for systolic pressure and 1 mm Hg for mean pressure until reaching the 5-year value of 104/58 (75) mm Hg. Diastolic pressure did not increase from 1 month to 5 years of age. Heart rate decreased with increasing age from the 2- to 3-week value of 153 to the 5-year value of 97 beats per minute. There was no difference in BP and heart rate values between boys and girls or among ethnic groups over the age ranges studied. Considering the high success rate in obtaining BPs in infants and small children, it appears that BP should be determined routinely, regardless of the age of the patients, when an oscillometric device is available.

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Blood pressure (BP) measurement is an important diagnostic tool in pediatric practice for the early detection of certain disease processes as well as the management of patients with alterations in BP. The conventional auscultatory

BP measurement technique is difficult to apply in newborns, infants, and small children due to faint Korotkoff sounds in these age groups.¹ Recommended methods^{2,3} and normal BP values^{2,3,6-9} have varied widely. Observer-related variation and/or bias may be an important contributor to the wide variation in normative values.^{8,11}

Automated BP measuring devices remove some of the above sources of variation,^{11,12} and an automated oscillometric device has been found to reflect directly measured arterial pressure quite accurately.¹² Of equal importance, they can be applied in the absence of a physician or nurse, thus minimizing environmental effects on BP. These devices are being used with increasing frequency in pediatric patient care areas. However, currently available normative data are derived from several studies in which conventional auscultatory methods or Doppler ultrasonic devices are used. It is necessary to establish normative data for oscillometric devices as well, since both the methodology and the environment for measuring BP differ from those above. It is not known if these differences might yield somewhat dif-

ferent normal values. Therefore, it was the purpose of this study to establish normative BP values for the first 5 years of age by the use of one of these devices, the Dinamap Monitor.

METHODS

The Dinamap Monitor Model 1846 (Critikon Inc, Tampa, Fla) was used in this study. This device detects motions of the BP cuff encircling the extremity. This motion is due to oscillation of the underlying artery. When a cuff inflated to a pressure level above systolic pressure is gradually deflated, three characteristic changes occur in the magnitude of oscillation. A sudden increase in amplitude occurs at systolic pressure, a further maximum increase in amplitude corresponds to mean pressure, and a gradual then sudden decrease in amplitude occurs at diastolic pressure.¹³ The accuracy of this device in reflecting direct arterial pressure has been demonstrated in the neonate,^{14,15} in infants and children,^{12,11} and in adults.¹⁶ The device has an automatic inflation-deflation control that allows multiple measurements without the potential effects of the presence of a physician or nurse and has an optional capability to record BP values.

Infants and children up to 5 years of age who were completely healthy or those who had only minor complaints without fever

Table 1.—Age, Sex, and Ethnicity of Study Population

Age Group*	No. of Patients	Sex, No. (%)		Ethnicity, No. (%)		
		M	F	White	Black	Hispanic
2 to 3 wk	105	49 (47)	56 (53)	55 (52)	27 (26)	23 (22)
1 to 5 mo	232	122 (53)	110 (47)	155 (67)	38 (16)	39 (17)
6 to 11 mo	183	80 (44)	103 (56)	152 (83)	4 (2)	27 (15)
1 y	245	109 (44)	136 (56)	205 (84)	6 (2)	34 (14)
2 y	212	112 (53)	100 (47)	166 (78)	12 (6)	34 (16)
3 y	193	103 (53)	90 (47)	151 (78)	8 (4)	34 (18)
4 y	226	100 (44)	126 (56)	185 (82)	9 (4)	32 (14)
5 y	158	72 (46)	86 (54)	134 (85)	2 (1)	22 (14)
Total	1554	747 (48)	807 (52)	1203 (77)	106 (7)	245 (16)

*Age at last birthday.

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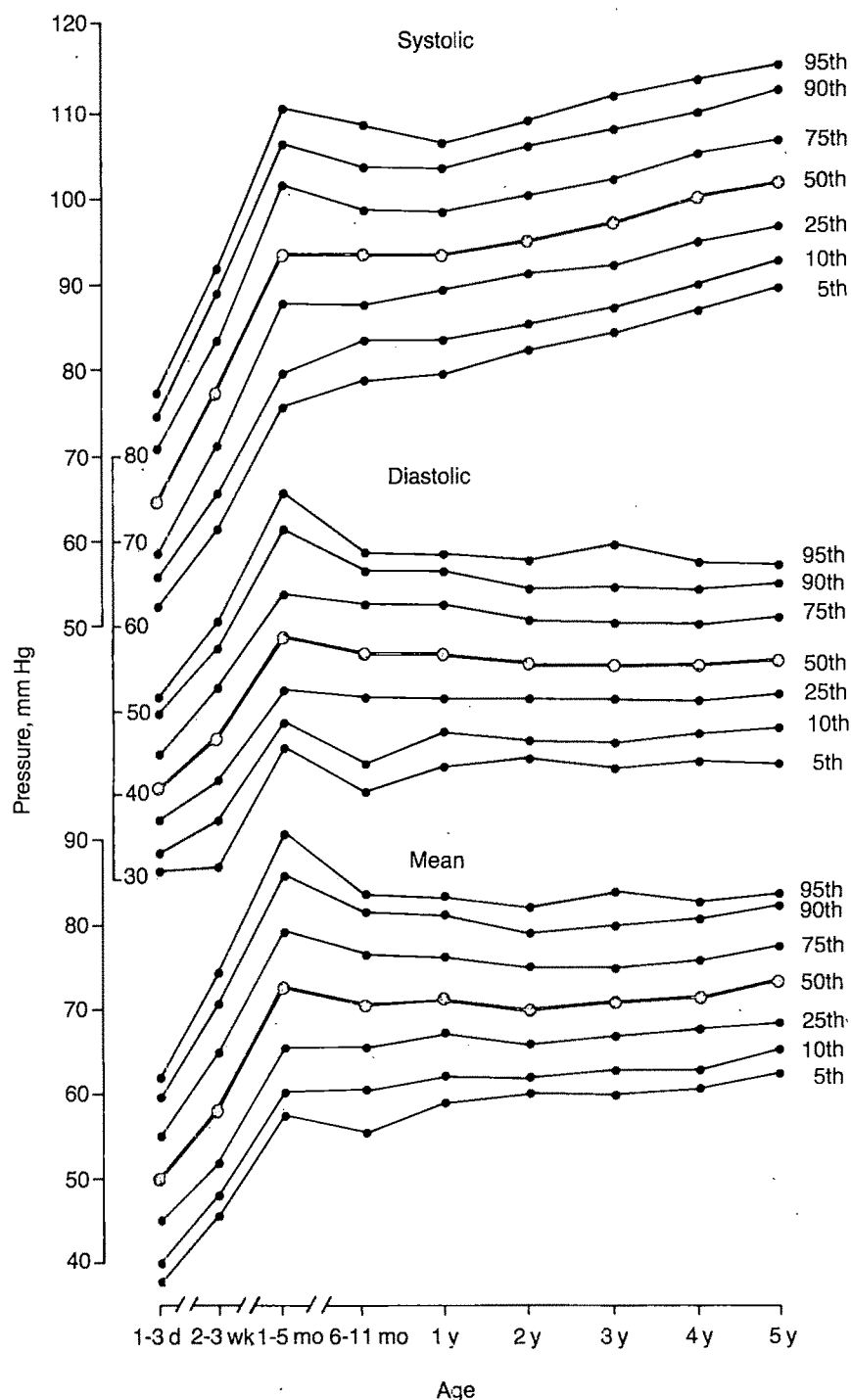


Fig 1.—Age-specific percentiles of Dinamap blood pressure values in patients 2 weeks to 5 years of age. The average of three readings is used. Values for 1- to 3-day-old newborns¹⁷ are included for completeness.

were recruited by a research nurse in the waiting room of pediatricians' offices and well-baby clinics in the San Antonio, Tex, area. Some patients were excluded from final analysis based on physicians' findings and diagnoses. Well siblings who accompanied patients were also recruited. Children

known to have cardiac, renal, metabolic, endocrine, neurologic, or pulmonary disease and those taking medications that might affect the BP were excluded from the study. There were a total of 1554 children in the study, including 747 boys (48%) and 807 girls (52%). Of these, 1203 were white (77%), 106

were black (7%), and 245 were Hispanic (16%) (Table 1).

Blood pressure cuffs were selected to be 40% to 50% of the measured circumference of the upper arm of each patient. This cuff size has been shown to permit accurate reflection of intra-arterial BPs in neonates,¹⁴ infants, and children¹² for Dinamap BP measurements. This cuff size coincides with that recommended by the American Heart Association for auscultatory blood pressure determination in children.⁵ To avoid apprehension, the research nurse carried out the blood pressure measurements in the waiting room before the children were seen by a uniformed nurse or physician. Infants were seated in parents' arms, supine on parents' laps, or semireclining in infant seats. Older infants and children were seated beside the parent. Distractions, such as a pacifier or bottle, reading, and talking, were used by the parents or the research nurse to maximize the child's cooperation.

Three BP and heart rate readings were obtained on each child with a 1-minute resting period between readings. Readings on children who became uncooperative or who were called into the examination room during the study were excluded from tabulation. Body weight and height were also recorded whenever available from the physician's office chart. The patient's age, ethnicity, sex, and position (supine, sitting, or semireclining) when BP was measured were recorded for statistical analysis. The statistical analysis was performed using the SPSS X program (SPSS Inc, Chicago, Ill). A one-way ANOVA followed by the Newman-Keuls Test was used when comparing three or more groups. When comparing two groups of data, Student's *t* test was used. Statistical significance was accepted at the .05 level. This study was approved by the Institutional Review Board of the University of Texas Health Science Center, San Antonio, and informed consent was obtained from one parent of each patient.

RESULTS

Sex and ethnicity of the study population are shown for each age group in Table 1. The mean ratio of cuff width to arm circumference (CW/AC ratio) was 0.46 with a range of 0.40 to 0.49. It was possible to obtain three acceptable BP readings in 87% of the infants younger than 3 years of age and in all children 3 years of age and older. Six percent of the children younger than 3 years of age were called into the examination room before the completion of three readings, and 7% of the children younger than 3 years of age did not cooperate enough to permit reliable BP readings.

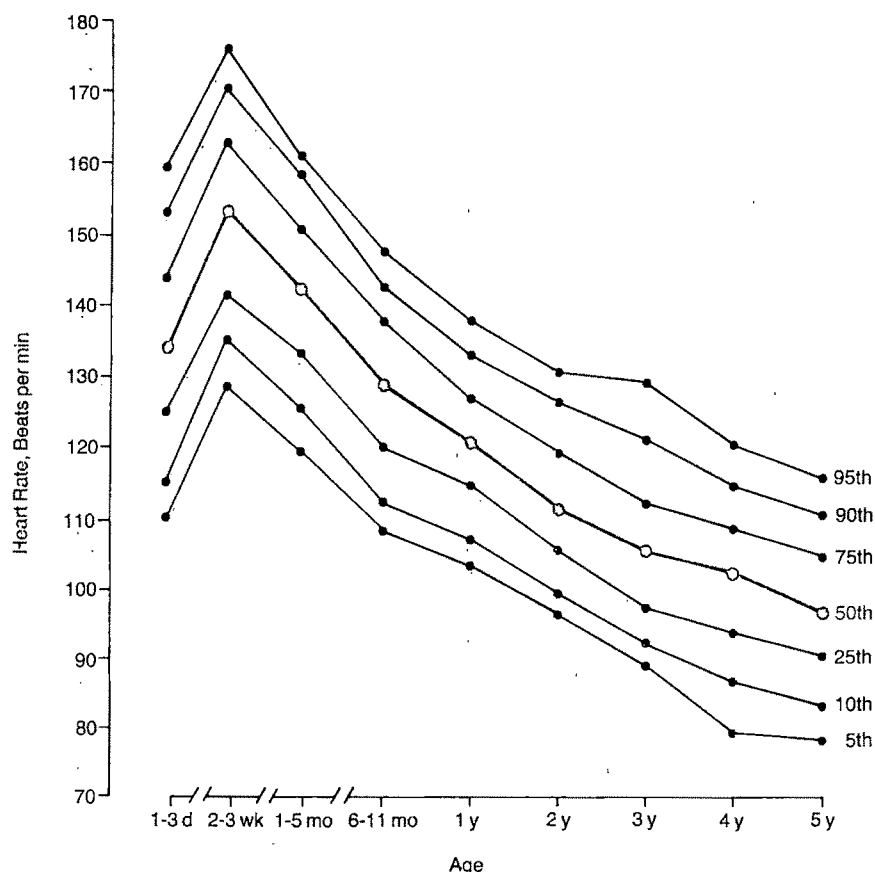


Fig 2.—Age-specific percentiles of heart rate by Dinamap Monitor in patients 2 weeks to 5 years of age. The average of three readings is used. Values for 1- to 3-day-old newborns¹⁷ are included for completeness.

Table 2.—Differences Between the First Blood Pressure (BP) Reading and the Average of Multiple Readings		
Age Group	Mean \pm SD	
	BP(1)* - XBP(1-2-3)†	BP(1) - XBP(2-3)‡
1 to 11 mo (n=415)		
Systolic	0.66 \pm 8.07	0.99 \pm 12.10
Diastolic	0.86 \pm 7.89	1.29 \pm 11.84
Mean	0.92 \pm 8.05	1.40 \pm 12.09
1 to 5 y (n=1034)		
Systolic	1.71 \pm 6.39§	2.56 \pm 9.59§
Diastolic	1.46 \pm 6.16§	2.19 \pm 9.26§
Mean	1.25 \pm 6.65§	1.88 \pm 9.98§

*BP(1) indicates the first BP readings.

†XBP(1-2-3) indicates the average of triplicate BP readings.

‡XBP(2-3) indicates the average of the second and third BP readings.

§BP(1) is significantly greater ($P < .05$) than XBP(1-2-3) or XBP(2-3).

For each age group, BP and heart rate did not differ between boys and girls ($P > .05$) and among different ethnic groups ($P > .05$). All patients 12 months of age and older and most of the patients 6 to 11 months old (98%) were

sitting when BP was measured. In infants 2 weeks to 5 months of age, BP values were taken with the infant in the sitting position (41.5%), the supine position (24.5%), or a semireclining position (34.0%). There was no statistically sig-

nificant difference in BP among the groups ($P > .50$ for systolic and mean pressures, and $P > .20$ for diastolic pressure). Because sex, ethnicity, and position were not found to contribute significantly to BP and heart rate, data were combined regardless of these variables and were expressed according to age.

Percentile values of the average BP are shown in Fig 1 and those of heart rate in Fig 2. Data from neonates 1 to 3 days old¹⁷ are also included for easier comparison and completeness. There is a rapid rise in systolic, diastolic, and mean pressures between the immediate neonatal period and the 1- to 5-month period (Fig 1). Systolic pressure did not rise from 1 month to 1 year of age. After 1 year of age, it began to increase at a rate of approximately 2 mm Hg per year until 5 years of age. Mean pressure values showed a similar trend to that of systolic pressure, but at a rate of approximately 1 mm Hg per year. Diastolic pressure did not rise from 1 month to 5 years of age (Fig 1).

In general, the first BP readings were greater than the average of the triplicate readings and that of the two latter readings. The average difference between the first reading and the average of the triplicate reading was smaller than the difference between the first and the two latter readings (Table 2). The difference was not statistically different in infants less than 12 months of age ($P > .20$), but was significantly different in children 1 year of age and older ($P < .05$) (Table 2). The correlation between systolic pressure and weight of the patient was fair ($r = .403$, $P < .0001$) and was slightly better than fair with age ($r = .378$, $P < .0001$). The correlation between diastolic ($r = .018$ to $.133$) and mean ($r = .105$ to $.133$) pressures and age, weight, or height was equally poor.

The heart rate decreased with increasing age, except for the immediate neonatal period (Fig 2). The first heart rate was 1 to 2 beats per minute lower than the average of the three readings and the two latter readings in children 3 years of age and older ($P < .05$), but not different in children younger than 3 years old ($P > .05$). There was a good negative correlation between heart rate and age, heart rate and weight, and heart rate and height ($r = .630$ to $-.772$, $P < .0001$).

COMMENT

This study establishes normative BP values in an office setting in infants and small children with the use of the Dinamap Monitor, which is widely used in pediatric patient care areas. A close correlation has been demonstrated between indirect BP values by the Dinamap Monitor and direct arterial BP values in infants and children.¹² There is also indirect evidence that supports the reliability and validity of Dinamap BP values. Systolic BP values in this study are in close agreement with those reported by the 1987 National Institutes of Health (NIH) Task Force,² which were derived from three independent studies using ultrasonic devices (Arteriosonde, Doppler ultrasound probe).

A report of BP values in Japanese children up to 3 years of age using the Arteriosonde is also in close agreement with the results of this study.¹⁸ Diastolic BP values of children 2 to 5 years of age taken as the Korotkoff phase IV reported by the NIH Task Force² agree closely with this study, but the values for infants 1 month to 1 year of age were 4 to 10 mm Hg lower than found by this study, in which the average increments of systolic and diastolic pressure in children 3 years and older were found to be similar to the findings of other epidemiological studies using a sphygmomanometer.^{19,20} In the age ranges studied, there appears to be no sex-related or ethnicity-related differences in BP (or heart rate), which is in agreement with other investigators.¹¹ Although normal BP values found in this study agree with large epidemiological studies,² we need to stress that the data were obtained in an office setting with the selection of patients not strictly adhering to epidemiological principles.

It should be stressed that the oscillometric equipment is merely a different detection device and we should still adhere to well-known guidelines^{1,2,5} of indirect measurement of blood pressure. Correctly selecting and placing the BP cuff on the patient, securing the cooperation of patients, preventing sudden movements of the extremity, and maintaining a quiet environment are all important requirements that must be met with any device, including an automatic one. It is mandatory to calibrate the

machine at regular intervals and to train personnel in the correct use of the device.

This study reconfirms earlier reports showing that systolic BP values are fairly well correlated with the weight and age of the patients,^{2,11} but the correlation is poor for diastolic and mean pressures. Although weight was slightly better correlated with systolic BPs than was age, we recommend that age be used to express normative values rather than weight for practical reasons. Similarly, although some people recommend that BP levels in growing children be related to height,⁶ we found that height was not better correlated to blood pressure levels than was age.

Some investigators recommend averaging two or three BP readings in children,^{6,21} but others do not.²² In children 11 to 17 years old, Hohn et al²² found no difference between the first BP readings and the average of three readings or that of the two subsequent readings. Using the auscultatory method in adult patients, the average of the triplicate measurements was found to be the same as a single measurement.²³

Obtaining three readings is not always possible in infants and children. Comparison of the first BP readings against the average of two latter readings and that of three readings reveals a certain pattern (Table 2). The first reading was not different from the average of multiple readings in infants younger than 1 year of age. After infancy, the first reading may be 1 to 4 mm Hg higher than the average of multiple readings. Apprehension associated with BP measurement may be responsible for the higher first reading seen in small children. Although the average of three readings may represent more basal and reproducible BP values,¹¹ in view of the relatively small clinical difference, we feel that one reading may be acceptable in daily practice as long as the above trend is taken into consideration in the interpretation of BP values.

This study also provides normative values for heart rate for this same group of children. The values have the advantage of being taken with minimal apprehension and, consequently, are likely to reflect the normal rate. The number of measurements made no difference in children younger than 3 years of age.

However, the first reading of the heart rate was 1 to 2 beats per minute lower than the average multiple-measurement values in children 3 years of age and older. The reason for this is not clear.

There are several advantages of the Dinamap Monitor over conventional or other noninvasive methods of BP measurement.^{12,13} Since it detects pressure oscillation, not sounds, the Dinamap Monitor can be used in neonates and small infants in whom Korotkoff sounds are usually too weak to give accurate readings. It can be used in a noisy environment or by a person with a hearing impairment. Observer-related variation and/or bias is completely eliminated; thus, there is no need for a long period of training personnel or a need to use a random zero device that is impractical in daily pediatric practice. A receptionist can easily be trained to use this device. The controversy over the choice between Korotkoff phase IV and phase V for diastolic pressure is not a problem. It also gives mean pressure and heart rate. An important drawback of this device is its relatively high cost for the average pediatrician. At the time this article was prepared, a Dinamap Monitor cost approximately \$3100.

The results of this study show that it is possible to obtain BP measurement in infants and small children using an automatic device. Currently, the NIH Task Force recommends routine BP determination by the auscultatory method in children 3 years of age and older.² It appears that routine BP determination should be practiced regardless of the age of patients when an oscillometric device is available. We found the Dinamap Monitor to be well accepted by most of our patient population. Three readings were possible in 87% of children younger than 3 years of age and in all children 3 years of age and older. This device was accepted by the patients 94% of the time for one reading in children younger than 3 years of age.

Our experience with oscillometric measurements of BP shows this to be more easily applicable in infants and small children than the conventional auscultatory method. Our normative data are generally in agreement with published values,² but show somewhat smaller variance. This may be because

our method precludes observer bias or variability, because a single consistent method and cuff size criterion were used, or because triplicate measurements were averaged. Finally, even with this method, problems and variables associated with indirect BP measurement still exist and should be controlled according to well-established guidelines.^{1,2,6}

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Dr Park and Ms Menard have no commercial or proprietary interest in the Dinamap Monitor or any financial interest (as consultant, reviewer, or evaluator) in the Dinamap Monitor.

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In Other AMA Journals

ARCHIVES OF INTERNAL MEDICINE

Components of a Smoke-Free Hospital Program

Alan F. Barker, MD; Jean R. Mosely, MN; Barbara L. Glidewell, MBS (*Arch Intern Med*. 1989;149:1357-1364)

Human Immunodeficiency Virus Transmission and Hemophilia

Margaret V. Ragni, MD, Pamela Nimorwicz, MSW (*Arch Intern Med*. 1989;149:1379-1380)

Insulinlike Growth Factors in Patients With Active Nephrotic Syndrome

Eduardo H. Garin, MD; Maria B. Grant, MD; Janet H. Silverstein MD

• The serum concentrations of insulinlike growth factors 1 and 2 (IGF-1 and IGF-2) were measured by specific radioimmunoassays in 25 nephrotic patients. The serum concentration of IGF-1 in nephrotic patients (mean \pm SEM, 169 ± 17 ng/mL) was significantly lower than that observed in 20 control subjects matched for sex and age (338 ± 36 ng/mL). The IGF-2 serum concentration was significantly lower in nephrotic patients (343 ± 22 ng/mL) than in control subjects (898 ± 80 ng/mL). The IGF-1 and IGF-2 150-kd and 45-kd carrier protein complexes were found in the urine of nephrotic patients, whereas there was no binding of radiolabeled IGF-1 or IGF-2 to IGF carrier proteins in the urine of control subjects. The low serum IGF-1 and IGF-2 levels observed in nephrotic patients could be partially due to the increased urinary losses of the IGF carrier proteins.

(AJDC. 1989;143:865-867)

Insulinlike growth factors (IGFs) are polypeptide hormones that mediate growth hormone action on cartilage cell metabolic activity and skeletal growth.¹ They circulate in the plasma specifically bound to one or more carrier proteins.² Free IGF represents less than 1% of the total IGF.³ The circulating IGF carrier protein complexes presumably serve as a storage site for these hormones in the body.²

Growth failure was frequently seen in edematous nephrotic children prior to the introduction of steroid therapy,⁴ and continues to be a problem for the patient who currently fails to respond to this mode of therapy. Because nephrotic

syndrome is characterized by increased glomerular permeability to plasma proteins,⁵ and because the IGFs are mostly bound to the carrier proteins, the urinary loss of the carrier protein could result in decreased plasma levels of IGFs, thus contributing to growth failure in those patients with persistent nephrotic syndrome.

The purpose of this study was to measure serum IGF-1 and IGF-2 levels in patients with active nephrotic syndrome and to determine the presence of the carrier proteins in the urine of the nephrotic patients.

PATIENTS AND METHODS

Twenty-five patients with active nephrotic syndrome and 20 control subjects matched for age and sex were included in the study. Seventeen patients had minimal lesion nephrotic syndrome, 5 had focal segmental glomerulosclerosis, and 3 had mesangial proliferative glomerulonephritis. There were 19 boys and 6 girls. Their ages ranged from 3 to 18 years, with a median age of 10 years.

All patients had active nephrotic syndrome, defined as massive proteinuria (>50 mg/kg per day or 40 mg/m² per hour or $3+$ by Albustix [Miles, Elkhart, Ind]) associated with low serum albumin levels (<0.25 g/L). All patients had normal serum creatinine concentration for age and had not received glucocorticoid therapy for at least 1 month prior to the study.

Serum concentrations of IGF-1 and IGF-2 were measured by the radioimmunoassay technique of Zapf et al⁶ after the growth factors were separated from their binding proteins by acid chromatography. The IGF labeled with iodine 125 was prepared in the laboratory of one of us (M.B.G.). The specific radioactivity of the labeled peptides was approximately 100 Ci/g. The radioactive iodine content was between 0.25 and 0.5 atoms per molecule of IGF.

Acid chromatography was performed on G-50 Sephadex columns (1×10 cm) (Pharmacia, Piscataway, NJ) using 0.5 mol/L of acetic acid. The fractions, eluting at 50% to 80%

bed volume, were combined, refrozen, lyophilized, and neutralized with 2 mL of 0.1 mol/L of ammonium bicarbonate. This again was refrozen, lyophilized, and brought into solution with 0.05 mol/L of phosphosaline buffer, pH 7.4. Aliquots of this were used for the radioimmunoassay with all samples made in duplicate.

For serum, the final dilutions were 1:200 and 1:400 for IGF-1 and 1:400 and 1:800 for IGF-2. Cross-reactivity of IGF-2 in the IGF-1 assay was 1%, and cross-reactivity of IGF-1 in the IGF-2 assay was 10%. Values in this study were corrected for this cross-reactivity. Internal standards in each assay were used to minimize interassay variation. These internal standards consist of three chromatographed sera, one from an acromegalic subject and two from control subjects. The latter were similarly used for the IGF-2 assay. Each internal standard was assayed at four dilutions in duplicate. The interassay variations for the IGF-1 and IGF-2 radioimmunoassay were 14.8% and 11.3%, respectively, while the intra-assay variations were 2.3% and 2.5%, respectively.

The presence of the carrier proteins for IGF-1 and IGF-2 in the urine of seven patients (four with minimal lesion nephrotic syndrome and three with focal glomerulosclerosis) and three control subjects matched for age was assessed. Urine was collected from each subject during a 24-hour period. The urine pH was maintained at neutrality during the collection. The urine was frozen, lyophilized, and then resuspended in 10 mL of distilled water. The sample was then filtered using Whatman GF/D microfiber filters (Whatman, Clifton, NJ) to remove any particulate matter. A 0.1-mL aliquot of urine was then incubated with either 30 000 cpm of ¹²⁵I-IGF-1 or ¹²⁵I-IGF-2 (specific activity: 100 Ci/g, radioactive iodine content was 0.25 to 0.5 atoms per molecule of IGF) for 24 hours at 4°C.

The reaction mixture was then applied to a 1.5×70 -cm column of Sephacryl S-200 that had been equilibrated with 0.05 mol/L of sodium phosphate (pH 7.4), 0.15 mol/L of sodium chloride, and 0.02% sodium azide and calibrated with human IgG (molecular weight [MW] = 156 kd), human transferrin

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From the Department of Pediatrics, Medical University of South Carolina, Charleston (Dr Garin), and the Departments of Pediatrics (Dr Silverstein) and Medicine (Dr Grant), University of Florida, Gainesville. Dr Garin is now with the University of South Florida, Tampa.

Reprint requests to Department of Pediatric Nephrology, University of South Florida, 1 Davis Blvd, Suite 404, Tampa, FL 33606 (Dr Garin).

(MW=88 kd), egg albumin (MW=45 kd), and chymotrypsin (MW=25 kd). The sample was then eluted with 0.05 mol/L of phosphate-buffered saline at 4°C with a linear flow rate of 16 mL/h. Fractions (1.6 mL) were collected and assessed for radioactivity. The binding proteins identified by this method were found to be specific for IGF-1 and IGF-2 in our previous studies.⁷

Serum albumin and creatinine levels were measured using a Technicon autoanalyzer II (Technicon, Atlanta, Ga). Urinary protein was determined using the sulfosalicylic-sodium sulfate test.⁸ Statistical analyses were performed using Student's *t* test for independent samples. Student's *t* tests were performed on the logarithms of the measured values of IGF-1 and IGF-2.

RESULTS

The serum concentration of IGF-1 in nephrotic patients (mean \pm SEM, 169 ± 17 ng/mL) was significantly lower than that observed in the control subjects matched for sex and age (338 ± 36 ng/mL, $P < .0001$). No significant differences were seen between the serum IGF-1 levels of patients with minimal lesion nephrotic syndrome (166 ± 24 ng/mL) and those of patients with other glomerulopathies (176 ± 30 ng/mL) (Table).

The mean IGF-2 serum concentration was significantly lower in nephrotic patients (343 ± 22 ng/mL) than control subjects (898 ± 80 ng/mL, $P < .001$). No statistically significant differences were found between IGF-2 serum levels of patients with minimal lesion nephrotic syndrome (338 ± 25 ng/mL) and patients with other glomerulopathies (356 ± 47 ng/mL).

The Sephacryl gel filtration of urine from seven nephrotic patients preincubated with ¹²⁵I-IGF-1 and ¹²⁵I-IGF-2 resulted in three peaks. The first peak had an apparent MW of 150 kd, the second peak had an MW of 45 kd, and the third peak represented excess unbound ¹²⁵I-IGF. All patients showed the same eluting pattern. A representative chromatogram is depicted in the Figure. There was no binding of radiolabeled IGF-1 and IGF-2 to IGF carrier proteins in the urine samples from the control subjects. Only unbound ¹²⁵I-IGF was detected on their chromatograms.

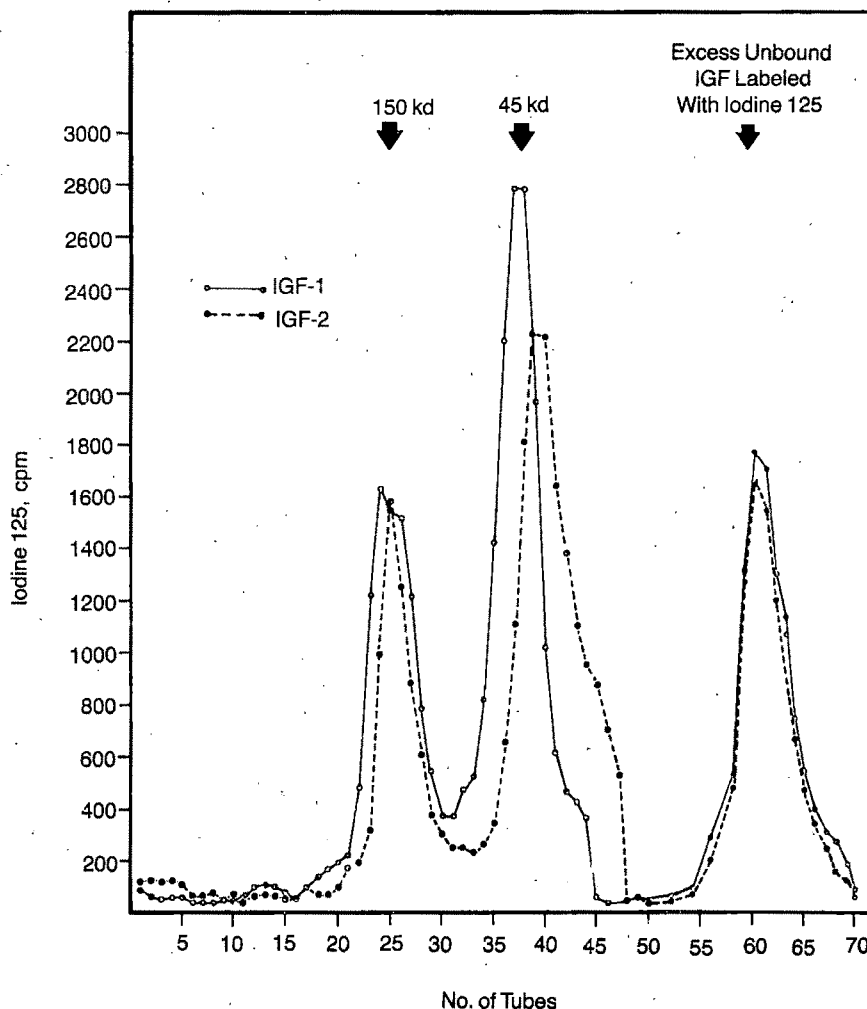
COMMENT

This study demonstrates that patients with active nephrotic syndrome

Insulinlike Growth Factor (IGF)1 and IGF-2 Serum Concentration in Nephrotic Patients		
	Mean \pm SEM	
	Nephrotic Patients (n=25)	Control Subjects (n=20)
IGF-1, ng/mL	$169 \pm 17^*$	338 ± 36
IGF-2, ng/mL	$343 \pm 22^\dagger$	898 ± 80

* $P < .0001$ compared with control subjects.

$^\dagger P < .001$ compared with control subjects.



The pattern of radioactivity eluting from a Sephacryl S-200 column is shown after incubation of insulinlike growth factors 1 and 2 (IGF-1 and IGF-2) labeled with iodine 125 with urine from nephrotic patients. The 150 kd represents the eluting peak for the 150-kd complex; the 45 kd indicates the eluting peak for the 45-kd complex. The third peak shows excess unbound ¹²⁵I-IGF-1 and ¹²⁵I-IGF-2.

have decreased serum levels of both IGF-1 and IGF-2 peptides. Furthermore, the decreased concentration was found regardless of the underlying pathologic features (minimal lesion nephrotic syndrome or other glomerulopathies). The low IGF-1 and IGF-2 levels could be due to decreased synthesis

of peptides, or increased urinary losses of the plasma carrier proteins, or both.

Insulinlike growth factor 1 is considered to be a sensitive marker of nutrition, particularly of dietary protein intake.⁹ Plasma levels of IGF-1 are known to be decreased in protein-energy malnutrition and after fasting.^{10,11} The nega-

tive nitrogen balance observed in patients with nephrotic syndrome may therefore explain the low IGF-1 serum levels found. However, periodic dietary recalls in our patients suggested adequate protein and energy intake. Moreover, though in negative nitrogen balance due to the massive proteinuria, nephrotic patients have increased hepatic protein synthesis.¹² Therefore, amino acids are available for the liver to synthesize albumin, IGFs, and other proteins, whereas protein wasting is seen in other organs, such as muscles. Thus, it is unlikely that nutritional factors alone can explain the decreased serum concentration of the IGFs.

Growth hormone regulates the hepatic production of the IGFs.¹³ The IGF-1 serum levels are far more growth hormone dependent than those of IGF-2. Children with nephrotic syndrome have normal basal and peak growth hormone levels to insulin provocation,¹⁴ suggesting that the decreased IGF-1 level is not due to inadequate growth hormone synthesis or release.

Insulinlike growth factor 1 and IGF-2 circulate in the plasma bound to specific carrier proteins.² Approximately 80% of the IGFs in normal plasma are carried as a part of a 150-kd MW complex that

appears to be under growth hormone control. The remainder of the IGFs are bound to a smaller complex with an estimated MW between 30 and 50 kd. The amount of this "45-kd" binding protein complex in plasma is less firmly linked to growth hormone than is the 150-kd form.

In this study, the 150-kd and the 45-kd carrier proteins were found in the urine of the nephrotic patients but not in control subjects whose urine did not have detectable amounts of these proteins. These increased urinary losses are due to the increase in glomerular permeability to plasma proteins, which is characteristic of patients with nephrotic syndrome.⁵ The 150-kd and 45-kd complexes were found in the urine of all seven patients with nephrotic syndrome, regardless of whether they were patients with minimal lesion nephrotic syndrome or other glomerulopathies.

Consistent with this finding, there were no significant differences between the serum levels of IGF-1 and IGF-2 in case patients with minimal lesion nephrotic syndrome and case patients with other glomerulopathies. A decrease in the plasma level of the active metabolite due to the urinary losses of

the active metabolite-carrier protein complexes has been described in case patients with nephrotic syndrome,¹⁵⁻¹⁸ in whom decreased plasma levels of vitamin D-binding globulin and transferrin have been reported.¹⁵⁻¹⁶ These carrier proteins have been found in the urine in large amounts, and the urinary losses have been associated with low plasma levels of ionized calcium and iron deficiency anemia.¹⁶⁻¹⁷

Growth is the result of complex interactions between nutrition, anabolic and catabolic factors, and the response of the target organs. Insulinlike growth factors are considered to be anabolic hormones. Their effectiveness is antagonized by IGF inhibitors. These appear to be proteins that are not measured by the IGFs' radioimmunoassay.¹⁸ Low serum levels of IGFs are found during conditions associated with growth disturbances. Thus, it is tempting to speculate that, in the patient with persistent nephrotic syndrome, poor growth could be mediated, at least in part, by a decrease in circulating IGFs due to increased IGFs' urinary losses.

We thank R. R. Humbel, MD, and R. Roesch, MD, Zurich, Switzerland, for providing the antibodies against IGF-1 and IGF-2, raised in rabbits.

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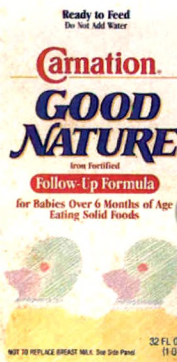
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... on the consumer promotion of infant formula.

There is a development that undermines your control over the infant's diet and health, and that undermines breastfeeding—the advertisement of formulas directly to the mother through TV, magazines and mail.

On June 1, the President of the American Academy of Pediatrics sent a letter to all Fellows of the Academy reaffirming its stance against consumer advertising, and expressing concern that other formula companies might follow Nestlé/Carnation.

This concern was justified. On June 15, it was announced at a press conference that Mead Johnson/Bristol-Myers will be producing an infant formula to be sold and marketed under the Gerber label. Part of the program is a multimillion-dollar budget for advertising the formula directly to mothers via TV and print.

Speaking at the press conference, Gerber Products Division President Robert L. Johnston, Jr., said that Gerber was entering the market because it had, "identified significant changes in usage that convinced us the timing was right. ..."

"First," he said, "there is a rapid decline in breast-feeding after mothers leave the hospital." And, "... parent decision regarding baby formula brand selection has grown. ..."

The irony is inescapable and appalling. In other words, because breastfeeding is declining, more infant formulas should be promoted to the mother. In other words, because some mothers are making feeding decisions on their own, even more mothers should follow suit.

When Nestlé/Carnation entered the marketplace and, again, when Mead Johnson/Bristol-Myers joined with Gerber, we reexamined the Ross philosophy of promoting SIMILAC® Infant Formulas. The result of our deliberations was an even deeper resolve to support the doctor/patient relationship.

Our philosophy remains unchanged. Ross Laboratories has no plans to resort to direct consumer advertising for SIMILAC and our other infant formula products.

We will continue as an ally of health care professionals by supporting your prerogative to prescribe and recommend products as training and experience dictate.

We stand behind you.

Richard W. Gast



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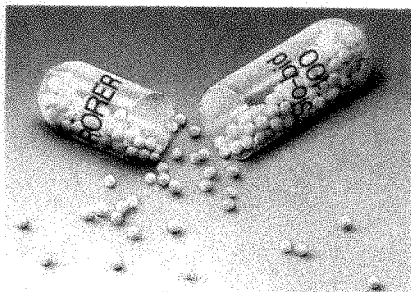
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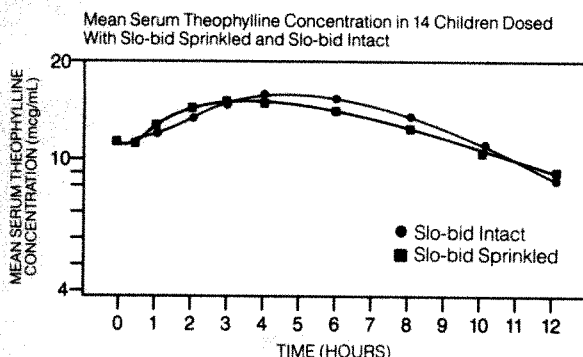
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INDICATIONS AND USAGE: For relief and/or prevention of symptoms from asthma and reversible bronchospasm associated with chronic bronchitis and emphysema.

CONTRAINDICATIONS: Slo-bid is contraindicated in individuals who have shown hypersensitivity to any of the components of this product. It is also contraindicated in patients with active peptic ulcer disease and in individuals with underlying seizure disorders (unless receiving appropriate anticonvulsant medication).

WARNINGS: Serum levels above 20 µg/mL are rarely found after appropriate administration of the recommended doses. However, in individuals in whom theophylline plasma clearance is reduced for any reason, even conventional doses may result in increased serum levels and potential toxicity. Reduced theophylline clearance has been documented in the following readily identifiable groups: 1) patients with impaired renal or liver function; 2) patients over 55 years of age, particularly males and those with chronic lung disease; 3) those with cardiac failure from any cause; 4) patients with sustained high fever; 5) neonates and infants under 1 year of age; and 6) those patients taking certain drugs (see PRECAUTIONS, Drug Interactions). Frequently, such patients have markedly prolonged theophylline serum levels following discontinuation of the drug.

Reduction of dosage and laboratory monitoring is especially appropriate in the above individuals.

Serious side effects such as ventricular arrhythmias, convulsions, or even death may appear as the first sign of toxicity without any previous warning. Less serious signs of theophylline toxicity (i.e., nausea and restlessness) may occur frequently when initiating therapy but are usually transient; when such signs are persistent during maintenance therapy, they are often associated with serum concentrations above 20 µg/mL. Stated differently, *serious toxicity is not reliably preceded by less severe side effects.* A serum concentration measurement is the only reliable method of identifying a potential for life-threatening toxicity.

Many patients who require theophylline exhibit tachycardia due to their underlying disease process, so the cause/effect relationship to elevated serum theophylline concentrations may not be appreciated.

Theophylline products may cause dysrhythmia and/or worsen preexisting arrhythmias and any significant change in rate and/or rhythm warrants monitoring and further investigation.

Studies in laboratory animals (minipigs, rodents, and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

PRECAUTIONS: General: On the average, theophylline half-life is shorter in cigarette and marijuana smokers than in nonsmokers, but smokers can have half-lives as long as nonsmokers. Theophylline should not be administered concurrently with other xanthine preparations. Use with caution in patients with hypoxemia, hypertension or with a history of peptic ulcer. Theophylline may occasionally act as a local irritant to the GI tract, although GI symptoms are more commonly centrally mediated and associated with serum drug concentrations over 20 µg/mL.

Information for Patients:

The physician should reinforce the importance of taking only the prescribed dose at the prescribed time intervals. The patient should alert the physician if symptoms occur repeatedly, especially near the end of a dosing interval. When prescribing administration by the sprinkle method, details of the proper technique should be explained to the patient.

Laboratory Test: Serum levels should be monitored periodically to determine the theophylline levels associated with observed clinical response and to identify the potential for toxicity. For such measurements, the serum sample should be obtained at the time of peak concentration, approximately 5-9 hours after the morning dose. It is important that the patient has not missed or taken additional doses during the previous 48 hours and that dosing intervals have been reasonably equally spaced.

DOSE ADJUSTMENT BASED ON SERUM THEOPHYLLINE MEASUREMENTS WHEN THESE INSTRUCTIONS HAVE NOT BEEN FOLLOWED MAY RESULT IN RECOMMENDATIONS THAT PRESENT RISK OF TOXICITY TO THE PATIENT.

Drug Interactions:

Drug-Drug: Toxic synergism with ephedrine has been documented and may occur with some other sympathomimetic bronchodilators. In addition, the following drug interactions have been demonstrated:

Theophylline with:	Increased serum theophylline levels
Allopurinol (high dose)	Increased serum theophylline levels
Cimetidine	Increased serum theophylline levels
Erythromycin, Troleandomycin	Increased renal excretion of lithium
Lithium carbonate	Increased serum theophylline levels
Oral contraceptives	Decreased theophylline and phenytoin serum levels
Phenytoin	Decreased serum theophylline levels
Rifampin	

Drug-Food: Taking Slo-bid immediately after a high-fat content meal such as 8 ounces whole milk, 2 fried eggs, 2 strips bacon, one bran muffin with butter, 2 ounces hash brown potatoes (about 789 calories, including approximately 49 gm of fat) may result in a decrease in the rate of absorption, but with no significant difference in the extent of absorption (see CLINICAL PHARMACOLOGY, Pharmacokinetics). The influence of the type and amount of other foods, as well as the time interval between drug and food, has not been studied.

Drug/Laboratory Test Interactions: Currently available analytic methods, including high-pressure liquid chromatography and immunoassay techniques, for measuring serum theophylline levels are specific. Metabolites and other drugs generally do not affect the results. Other new analytic methods are also now in use. The physician should be aware of the laboratory method used and whether other drugs will interfere with the assay for theophylline.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies have not been performed with theophylline.

Chromosome-breaking activity was detected in human cell cultures at concentrations of theophylline up to 50 times the therapeutic serum concentrations in humans. Theophylline was not mutagenic in the dominant lethal assay in male mice given theophylline intraperitoneally in doses up to 30 times the maximum daily human oral dose.

Studies to determine the effect on fertility have not been performed with theophylline.

Pregnancy: Pregnancy Category C—Animal reproduction studies have not been conducted with theophylline. It is also not known whether theophylline can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Theophylline should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Theophylline is distributed into breast milk and may cause irritability or other signs of toxicity in nursing infants. Because of the potential for serious adverse reactions in nursing infants from theophylline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:

Safety and effectiveness of Slo-bid Gyrocaps administered:

1. Every 24 hours in children under 12 years of age, have not been established.
2. Every 12 hours in children under 6 years of age, have not been established.

ADVERSE REACTIONS: The following adverse reactions have been observed, but there has not been enough systematic collection of data to support an estimate of their frequency. The most consistent adverse reactions are usually due to overdosage.

Gastrointestinal: nausea, vomiting, epigastric pain, hematemesis, diarrhea.

Central Nervous System: headaches, irritability, restlessness, insomnia, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions.

Cardiovascular: palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, ventricular arrhythmias.

Respiratory: tachypnea.

Renal: potentiation of diuretics.

Other: alopecia, hyperglycemia, inappropriate ADH syndrome, rash.

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- 125 mg—Opaque white (cap) and opaque white (body) capsule with 125 printed in red
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- 300 mg—Opaque white capsule with 300 printed in red

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The Pediatric Forum

This department of AJDC is reserved for comment, criticism, observation, and discussion of "issues of current concern and importance for children's health." The Editor encourages our readers to express themselves on a variety of topics and issues. Further, we encourage the submission of unique and brief clinical and scientific observations that do not fulfill the criteria for original articles.

Campylobacter pylori Gastritis and Peptic Ulcer in Children

Sir:—We read with great interest the article by Kilbridge et al¹ in the December 1988 issue of *AJDC* on *Campylobacter pylori* (CP)-associated gastritis and peptic ulcer disease in children, which are becoming growing problems in pediatric gastroenterology. In fact, according to some authors CP is present in antral biopsies of up to 32%^{2,3} of children with recurrent abdominal pain severe enough to require gastroscopy. Even if the prevalence of CP infection is known to increase with age and, therefore, it is expected to be lower in the pediatric population, in children with primary gastritis the percentage of CP infection is as high as 60% to 80%^{4,5} and quite similar to the rate found in adults.

In a retrospective study we carried out on all gastroscopies performed in our center from 1983 to 1987, only 58 patients (8.6%) with primary gastritis were found, but in 70.7% of them CP was identified when the histological slides were reviewed. We feel that this figure, like the 55% reported by Kilbridge et al, underestimates the real prevalence of CP infection. In fact, we used to take biopsy specimens only from those gastric antra showing some changes at endoscopy, but we are now aware, as Kilbridge et al pointed out, that CP can colonize a normal-appearing antrum. The low figures reported could be due to the fact that their study was retrospective. We would like to emphasize the high prevalence of the CP infection in children that, in a prospective study we are presently conducting, is reaching more than 90% in children with primary gastritis or peptic ulcer disease.

Two points in the article by Kilbridge et al are of particular interest:

1. There was a predominance of chronic infiltrate antral CP gastritis in children, with less diffuse acute inflammatory component than in

adults. Their hypothesis that this represents an earlier phase of infection is attractive but does not seem to be confirmed by some of our observations.⁶ In fact, we too observed a higher prevalence of chronic gastritis in children with CP infection (26 cases vs 16 with acute inflammatory infiltration), but after amoxicillin treatment, which cleared the infection in 85% of the children and healed the gastritis in 67%, we observed a recurrence in 73% of the patients 3 months after stopping the treatment. We think that these recurrences could be considered as an early phase of infection since 3 months earlier gastritis was not present. Sixty percent of these children who suffered a relapse showed an acute gastritis.

2. There was a high relapse rate (80%) of duodenal ulcer in patients with CP gastritis. This finding may indicate that CP presence in antral mucosa portends an unfavorable prognosis. In a long-term follow-up study of children with peptic ulcer treated with ranitidine, we observed a relapse rate of 47% of 31 patients; CP was present in 85% of children who had a relapse but only in 29% of those who did not.⁷

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Sir:—Although a rapidly expanding body of literature provides much information concerning the prevalence and the significance of CP in adults,¹ there is little information as to whether the association of this organism with histologic gastritis represents in childhood a causal relationship or merely an association. After reading the article by Kilbridge et al, we were stimulated to report in brief our preliminary data to address this question.

Recently we initiated a prospective study in which we attempted to identify CP in antral biopsies obtained from children undergoing upper gastrointestinal tract endoscopy for chronic abdominal pain, hematemesis, vomiting, and unexplained iron-deficiency anemia. To date, complete evaluation has been obtained on 24 children.

In 11 of the 24 antral biopsies, the light microscopy showed evidence of chronic gastritis, which was characterized by a diffuse inflammatory cell infiltration of the lamina propria consisting of plasma cells and lymphocytes. *Campylobacter pylori* was detected by means of histological stains and culture in 10 of the 11 children with chronic gastritis. None of the 13 patients with histologically normal antral mucosa had CP demonstrated on their antral biopsy specimens. The presence of the bacterium was associated with mild as well as moderate to severe inflammatory changes of the antral mucosa. The association of CP even with mild gastritis provides further support that this organism represents an inciting factor for antral gastritis in children.

Surprisingly, the antral biopsies did not indicate the presence of CP as a marker of "active" histological gastritis. In fact, the histological appearances were never associated with signs of activity.² Kilbridge et al suggested that the "inactive" chronic inflammation observed in the younger subjects in their study may represent an earlier phase of infection.

In our study, patients with CP-associated gastritis were older (mean age, 9.8 years) than those who did not present this condition (mean age, 6.7 years). As previously described in adults,³ it is possible that "active" chronic gastritis due to CP may be limited also in children to a patchy distribution and may not be present at the site of detection of the organism. Finally, six patients who received a 4-week course of monotherapy with amoxicillin trihydrate (50 mg/kg per day in three divided doses) exhibited eradication of the organism, which was associated with a marked improvement or complete resolution of the inflammatory changes of the gastric mucosa. After 6 to 18 months of cessation of therapy, the patients continue to be asymptomatic.

As Kilbridge et al point out, additional prospective long-term follow-up studies may help to clarify further the role of CP in the pathogenesis of antral gastritis in children.

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In Reply.—Chiesa et al and Oderda et al agree with us regarding the high prevalence of CP infection and its relationship to antral gastritis and

duodenal ulcer.

The highly effective results of antimicrobial therapy reported by Chiesa et al are interesting. To date, we have been unsuccessful in eradicating CP with amoxicillin monotherapy. Our results are in agreement with recently reported adult studies by Rauws et al,¹ as well as pediatric studies by De Giacomo et al.² The latter group had no success in eradicating CP or improving the underlying gastritis in their pediatric patients. The experience cited above by Oderda et al also indicates failure to achieve permanent eradication of the organism with ampicillin. We look forward to the publication of the study done by Chiesa et al. Perhaps we may be able to determine why we and others have not been successful in our efforts to eradicate CP. We agree with Dr Oderda and his colleagues that children with CP gastritis and duodenal ulcer are very likely to suffer ulcer relapse if they are treated with standard H₂ antagonist therapy alone and the CP infection is not eradicated.

Both Chiesa et al and Oderda et al have additional observations regarding the relative roles of acute and chronic inflammation in CP gastritis. In pathologic parlance, the term *active gastritis* as used by Chiesa et al means acute inflammatory cells are present in the tissue. They did not observe active gastritis in any of their CP infections; all the gastritis they observed was histologically chronic inflammation. Their experience again differs from ours and from the other published series of CP gastritis in children,^{3,6} where both chronic and acute inflammation are described. Oderda and colleagues also observed, as we did, that both chronic and acute inflammation are present, with chronic gastritis predominating. Oderda et al suspect that acute inflammation is present from the start of CP infection in some patients, since they observed acute gastritis within 3 months of reinfection with CP.

European gastroenterologists, such as Chiesa and Oderda, appear to be more interested than their American colleagues in CP and more convinced of its pathogenic role in upper gastrointestinal tract disease.

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Hyperuricosuria and Microhematuria in Childhood

Sir.—Microhematuria is a common finding in pediatrics that frequently requires multiple diagnostic procedures¹ to determine its cause, which in many cases remains uncertain.

Among the multiple possible causes, Stapleton et al² pointed out the role hypercalciuria would play in the pathogenesis of certain types of microhematuria. We have found an association between hyperuricosuria and microhematuria in five otherwise-healthy children. We think that a pathogenic mechanism is operative that is similar to the one reported by Stapleton et al² for microhematuria secondary to hypercalciuria. The small number of patients tested only suggests this possibility and the pilot experience reported herein will require further investigation.

Patients and Methods.—Five children (2 boys and 3 girls), whose ages ranged from 4 to 9 years, were selected from a total of 139 patients with microhematuria because they presented abnormally high levels of uricosuria with no other underlying cause.

In one of the children the onset of the disorder was accompanied by gross hematuria and colic pain (with no calculi expulsion) and microhematuria that persisted after this episode. In the remainder of the patients the condition was asymptomatic and the persistence of microhematuria was assessed by examination of at least five consecutive urine specimens.

Renal function (serum urea and creatinine levels and creatinine clearance) was normal in all patients. Results of coagulation studies, 24-hour calciuria measurement, intravenous pyelography, and cystourethrography were all normal. Diseases causing hypouricemia were eliminated and the possibility of exposure to drugs or heavy metals was also considered.

Microhematuria was defined by the presence of more than 15 red blood cells per high-power field in fresh urinary sediment

Table 1.—Analytical Findings					
	Patient No.				
	1	2	3	4	5
Age, y	4	4	9	4	7
Sex	M	F	M	F	F
Hematuria*	MH/mh	mh	mh	mh	mh
Serum uric acid, $\mu\text{mol/L}$	125	90	125	90	155
Uricosuria, $\text{mg}/1.73 \text{ m}^2 \text{ per day}$	1252	1384	1104	1325	1220
Fractional excretion of uric acid %	26.52	28.8	22	35.23	24.76

*MH indicates macroscopic hematuria; mh, microscopic hematuria.

Table 2.—Analytical Data in the Evolution of the Patients in Whom Microhematuria Resolved				
	Patient 3		Patient 5	
	Initial	Final	Initial	Final
Hematuria*	+	—	++	—
Uricosuria, $\text{mg}/1.73 \text{ m}^2 \text{ per day}$	1104	445	1220	633
Uric acid, mmol/L	125	132	155	150
Follow-up, mo	6	...	22	...

*Plus and minus signs are dipstick readings.

(counted in a Neubauer chamber) in at least five consecutive voidings.

The measurement of blood and urinary uric acid levels was done by the uricase enzymatic method.⁸

Results. — Increased uricosuria; measured in milligrams per 1.73 m^2 per day, and fractional excretion of uric acid higher than 20% were noted in all of our patients. Results of the examination of the urinary sediment in patients 1, 2, and 3 by phase-contrast microscopy⁴ were consistent with hematuria of nonglomerular origin.

Clinical and analytical data collected at the time of diagnosis are shown in Tables 1 and 2.

Two of the children (patients 2 and 3) with microhematuria and a slight elevation of fractional excretion of uric acid were maintained on a moderately restricted purine diet. This lowered the uricosuria to its normal range, and microhematuria disappeared from at least five repeated samples obtained within a 1-week interval.

The other three patients did not follow the diet adequately, hyperuricosuria persisted, and microhematuria did not resolve.

Comment. — Hematuria defined as more than 15 red blood cells per high-power field (microscopic or mac-

roscopic) is a frequent finding in childhood. Its prevalence has been estimated at 0.4%⁹ and it is a common cause of pediatric ambulatory visits (1.3 per 1000 patients).⁶

Microhematuria of the nonglomerular type has been associated with hypercalciuria that is possibly due to microscopic calculi originating in the tubular epithelium.² This hematuria resolves when calciuria returned to normal levels after adequate treatment.

A normal uricosuria value in childhood has already been defined (measured in milligrams per 1.73 m^2 per day) as a more accurate criterion that seems to increase proportionately with age variations and in relation to weight and height. For normal Spanish children the median (SD) value for uric acid fractional excretion is $643.66 (\pm 190) \text{ mg per } 1.73 \text{ m}^2 \text{ per day}$.⁷

We have found increased levels of uricosuria in five patients, accompanied by persistent microhematuria (and an episode of macroscopic hematuria in one of them), but with no evidence of urolithiasis in any of the cases, at the time of diagnosis and during follow-up. Other studied measures were all normal.

Erythrocyte structures, in the three cases in which they were observed,

were of the nonglomerular type that is seen in hypercalciuria, suggesting a similar pathogenic mechanism.

The fact that uricosuria decreased in two of our patients after institution of a purine-restricted diet, along with the disappearance of microhematuria, seems to confirm this hypothesis.

Hyperuricosuria seems to be another possible cause of microhematuria in childhood (although it has not yet been reported in the literature), as suggested by the results of our study. We advise the measurement of uricosuria in those children who have persistent microhematuria and normal clinical and analytical data.

The long-term risk for the development of urolithiasis in these patients with hyperuricosuria and hematuria remains unknown, requiring a more extensive follow-up. The detection of high values of uricosuria suggests that assay of renal tubular handling of uric acid is necessary in these patients.

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Updating Immunization Status at Discharge

Sir. — Several benefits of a strategy to immunize children at the time of discharge from a community hospital were suggested recently.¹ We assessed the costs and feasibility of implementing this program in our hospital over a 4-week period.

Age Group and Health Insurance Status of All Children Admitted to the Hospital and Those Immunized at Discharge

Age Range, y	All Patients Admitted to Hospital			Patients Immunized at Discharge		
	No. of Patients	% of Total Patients	Indigent Patients, %	No. of Patients	% of Age Group	Indigent Patients, %
0-2	53	68	38	8	15	50
2-4	13	17	31	2	15	50
4-6	7	9	29	0
6-8	2	3	50	1	50	100
>8	3	4	67	0
Total	78	...	37	11	...	55

Materials and Methods.—The study was conducted at the Women's and Children's Hospital of the University of South Alabama Medical Center in Mobile during the month of November 1988. Our facility is a regional tertiary care center. Overall, 42% of the medical expenses for admissions to the pediatric floor are covered by private insurance carriers and 20% are covered by Medicaid. Thirty-eight percent of the patients are indigent.

The immunization status of all children admitted to the general pediatric service was assessed. The residents were asked to verify the information by asking the parents to bring in immunization records or by making telephone calls to previous health care providers. The dates and form of verification were recorded on a separate sheet for this prospective study. Each patient for whom the immunization status was not up to date according to the American Academy of Pediatrics recommendations² was considered eligible for immunization at discharge.

Live vaccines were withheld from children with suspected or documented viral illness to avoid interference. Oral polio vaccine was supplanted by inactivated poliovirus vaccine to avoid the contraindication of diarrhea and the remote risks to other patients in the event a patient had to be readmitted. Informed consent was required, and small children received prophylactic acetaminophen.

Results.—A total of 13 patients (17% of all hospitalized study patients) did not have up-to-date immunizations. Immunizations were given to 11 of the patients; 2 patients were not immunized. One of these patients was a 2-month-old infant admitted for "rule-out sepsis," and immunization-induced fever could have prompted another workup and admission. Immunization after discharge was recommended in the other patient because the experimental policy would have meant an undue delay in discharge.

The number of patients, their respective age groups, and their medical

insurance status are listed in the Table. A total of nine doses of diphtheria and tetanus toxoids and pertussis vaccine, eight doses of inactivated poliovirus vaccine, five doses of *Haemophilus influenzae* type b diphtheria conjugate, and two doses of measles-mumps-rubella vaccine were given. The total cost of the vaccines was \$312, of which \$158 would have been covered by insurance (all Medicaid patients in our survey). A higher proportion of indigent patients (55%) were found in the group needing immunization compared with all children admitted to the hospital (37%). None of the children immunized had an identifiable primary care physician.

Comment.—Although our study was limited to a few patients in a 1-month period only, it showed that in our setting about 14% of patients would benefit from a discharge immunization policy. None of the patients had any complications from the immunizations, nor did the immunization result in further telephone calls or visits to the emergency department. Results from our preliminary study suggest that such immunization programs are feasible and safe and may provide an important function in hospitals serving indigent patients. Another potential benefit from such a program might be from teaching residents on a "learn as you do" basis about this important aspect of preventive pediatrics.

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We thank our residents and students for transporting the vaccines and Vista Woodruff, LPN, for help in making the vaccines available.

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Prevention of Accidental Extubations in Newborns

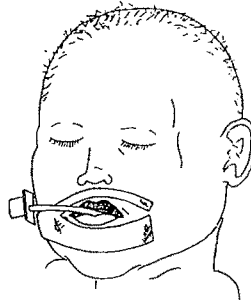
Sir.—We read with interest the article by Brown¹ that appeared in the November 1988 issue of *AJDC* concerning accidental extubations in newborns.

We have used a variation of the pinning method for endotracheal tube stabilization at our nursery for the past 4 years. This method is illustrated in the Figure. Our method is used exclusively in orally intubated newborns. The newborn's face is prepped with a tincture of benzoin, and elastic tape (Elastikon, Johnson and Johnson, New Brunswick, NJ) is used as illustrated. A 2.5-cm safety pin (presterilized) is carefully placed to minimize mechanical compromise of the endotracheal tube lumen. Shiley (Shiley Inc, Irvine, Calif) uncuffed pediatric oral/nasal Murphy endotracheal tubes are primarily used. It does take an initial orientation to become familiar with the technique, but once learned, respiratory therapists and nurses have reported minimal morbidity. We have found no problems with suctioning past the pin. In even 2.5-mm (inside diameter) tubes a 6.0F catheter can be inserted easily if care is taken to secure the pin properly. We have seen no incidents of downward migration of the endotracheal tube, ie, accidental displacement of the tube to the carina or into the right main-stem bronchus.

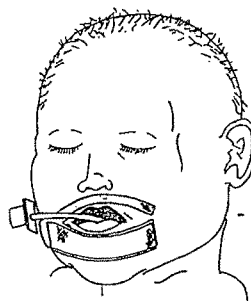
Using Dr Brown's lead, we retrospectively reviewed 37 patients undergoing ventilation in our neonatal intensive care unit. We initially looked at 22 patients selected consecutively over the last 2 months and found no accidental extubations over a period of 94 intubation days. We then selected an additional 15 patients at random over the last 2 years (September 1986 to September 1988). Of a total of 405 intubation days there were 12 recorded accidental extubations or 3.0 extubations per 100 intubation days. Of interest was that only 4 (10.8%) of 37 patients accounted for all of the extubations, and 2 patients (163 intubation days) accounted for 9 extubations. Consistent with Dr Brown's findings, both were extremely low-birth-weight infants. All of their extubations occurred after the first



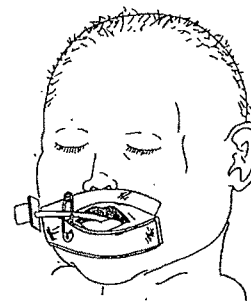
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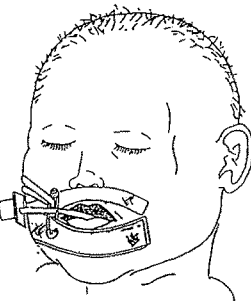
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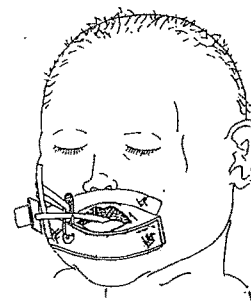
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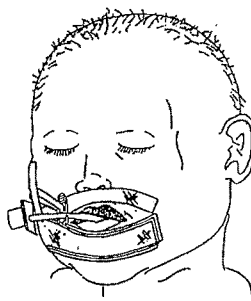
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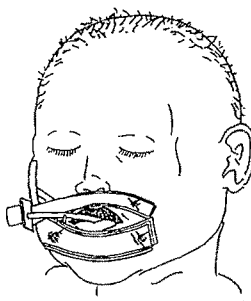
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Technique of securing the oral endotracheal tube.

month of life. If we looked only at the first month of life, we found only 3 accidental extubations of 298 intubation days or 1.0 extubation per 100 intubation days.

During our residency and fellowship training we have been involved with neonatal services at five separate university centers. Anecdotally, we have been uniformly impressed that this method in comparison with several variations on a taping method appeared superior.

We reviewed our numbers to bring attention to a particular technique of securing endotracheal tubes in newborns, and our experience with this technique as used in a community-based neonatal intensive care unit setting.

The method described in Brown's article appears quite effective. It would be interesting to see a prospective comparison of these two methods.

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Simultaneous Transient Hyperphosphatasemia in a Set of Twins

Sir.—The diagnostic features of benign transient hyperphosphatasemia are (1) patient age of less than 5 years; (2) variable, usually unrelated symptoms; (3) no physical evidence for bone or liver disease; (4) no other biochemical or laboratory evidence for bone or liver disease (including normal isoenzymes, if test is done); and (5) a return to normal serum alkaline phosphatase level within 4 months with no sequelae.¹ The cause is unknown but proposed mechanisms include malnutrition, drug induction, viral infection, and transient impeded clearance of serum alkaline phosphatase.¹ The two patients described herein are, to our knowledge, the first set of twins who developed the syndrome simultaneously.

Patients and Methods.—These 11-month-old white male twins were well until an age of 9 months, when they developed severe diarrhea. Stool cultures from both were positive for *Salmonella*. No antibiotics were given. They continued to have frequent loose stools over the next 2 months, despite outpatient

trials of taking casein hydrolysate formula (Pregestimil), a liquid containing kaolin, pectin, hyosyamine sulfate, atropine sulfate, and scopolamine hydrobromide (Donnagel), and *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* (Lactinex), and trying elimination diets. Irritability, diarrhea, poor weight gain, and parental anxiety prompted workup.

On physical examination, both twins appeared alert, happy, and well hydrated. Both were at the 10th percentiles for height, weight, and head circumference. The only abnormalities noted were mild rhinorrhea and otitis media in both patients. No abnormal liver or bone findings were noted.

Results.—Both patients had the following tests done, with each having negative or normal results: complete blood cell count; glucose, urea nitrogen, creatinine, sodium, potassium, chloride, uric acid, calcium, cholesterol, creatine phosphokinase, aspartate aminotransferase, alanine aminotransferase, γ -glutamyltransferase, bilirubin, lactate dehydrogenase, total protein, albumin, IgG, IgA, IgM, carbon dioxide, serum pH, folate, carotene, phosphorus, and 1-hour blood xylose levels; stool tests for rotavirus, bacterial culture, parasites, pH, blood, and clintest; and a sweat test. Twin B also had a normal value for his IgE level, and a qualitative stool test for trypsin produced a normal result.

Twin A's initial alkaline phosphatase level was 2885 U/L (Table). Twin B's initial alkaline phosphatase level drawn at the same time was 896 U/L. Four weeks later, twin A's level was 303 U/L and twin B's level was 355 U/L. Both patients had normal levels 8 weeks later.

Both twins were given normal diets for their age. The mother was instructed to decrease their water and juice intake and to use whole milk to satisfy thirst. The otitis was treated with cefaclor. The diarrhea resolved and weight gain was documented. The parents reported no further episodes of diarrhea.

Comment.—Twin B's initial alkaline phosphatase value was lower than twin A's and probably represented our documenting the elevation on its way back to normal levels. It seems clear to us that their syndrome occurred simultaneously. The cause for transient, benign hyperphosphatasemia remains unknown. Our recent review¹ and letter² argued against the leaking of enzymes from severe liver and/or bone damage as a cause, while postulating that impeded clearance of the enzyme might be more plausible. The results reported herein

Alkaline Phosphatase Levels*			
	Alkaline phosphatase, U/L		
	Initial	After 4 wk	After 8 wk
Twin A	2885	303	403
Twin B	896	355	433

*Normal values in our laboratory in infants under 12 months of age are 170 to 450 U/L.

suggest that a genetic predisposition for impeded clearance of alkaline phosphatase may be triggered by an exogenous insult, such as a viral infection, acute nutritional deficiencies, or drugs. This, of course, does not explain the transient nature of the syndrome nor does it explain why 14 of 68 patients described were normal controls without evidence of insults of any kind (unless insults were so trivial as to be overlooked by the clinicians).¹ The syndrome continues to be an enigma, but careful clinical and laboratory observations may shed some light in the future.

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Very-Low-Birth-Weight Infants

Sir.—In the January 1989 issue of *AJDC*, Georgieff et al¹ report on more aggressive early neonatal nutritional management, changes in cardiopulmonary management, and a lower incidence of chronic disease in 1986 compared with 1982. This has promoted earlier onset of, and a more rapid rate of, postnatal growth that extends to the first year of follow-up. The authors compared 37 of 82 very-low-birth-weight infants born in 1982 with 29 of 46 infants born in 1986, representing follow-up rates of 57% and 64%, respectively.

However, only 32 of the infants born in 1982 and 18 of those born in 1986 were followed up until 2 years of age. Thus, 32 (39%) of 82 infants and 18 (39%) of 46 infants received follow-up until 1 year of age. The authors compared the neonatal data of the 47

infants born in 1982 with those of the 29 infants born in 1986 and came to the conclusion that a more aggressive early nutritional regimen, changes in cardiorespiratory management, and a lower incidence of severe medical complications affected later growth of the infants.

I have serious concerns about reporting data on the outcome of about one third of a population when two thirds of the population have been unavailable for follow-up. I also have serious concerns about coming to conclusions over changes in neonatal care when only 57% and 64% of the neonatal patients' data have been compared. To evaluate whether changes in neonatal care have occurred, all the children in the neonatal intensive care unit during 1982 and 1986 should have been evaluated concerning clinical characteristics, nutrition, and neonatal morbidity. This information is available in the neonatal charts and is unrelated to how many children were later followed up. In the event that this is not done, the neonatal variables of those followed up should at least be compared with the neonatal variables of those unavailable for follow-up.

I do not see how the authors could have based their conclusion on a follow-up of less than one third of a neonatal intensive care unit cohort at 1 year of age. The experience of most neonatal intensive care units is that with the increased survival of extremely-low-birth-weight infants, morbidity, including chronic lung disease, has increased from 1982 to 1986. The authors found the opposite. These conclusions might be related to the fact that the total neonatal intensive care unit population was not analyzed and the follow-up rate was so poor.

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1. Georgieff MK, Mills MM, Lindeke L, Iverson S, Johnson DE, Thompson TR. Changes in nutritional management and outcome of very-low-birth-weight infants. *AJDC*. 1989;143:82-85.

In Reply.—Dr Hack's first point, regarding providing hospitalization data on all very-low-birth-weight infants, including those not seen on follow-up, does not pertain to the interpretation

of our study results. As stated in the report, the purpose of our study was to assess growth differences at follow-up between two cohorts of infants with similar size and degree of illness who were treated 4 years apart. As described in Table 1 of the report, the cohorts were carefully matched for gestational age, weight, and degree of illness at presentation. Presentation of data on infants not subsequently seen on follow-up would serve no useful purpose in elucidating the neonatal factors that influenced follow-up growth rates of those seen.

The second point, regarding the low follow-up rate at 1 year, was a difficult one during analysis of the study results. We carefully stated in the report that there might be selection bias in those children who returned at 1 year, and that the 1-year results of the two groups may not be strictly comparable. We acknowledged the difficulty in interpreting such potentially misrepresentative low numbers in the last paragraph of the "Results" section. We used this as a rationale to combine the 12 months' corrected age data from the two age groups to demonstrate the poor developmental outcome associated with poor growth. Dr Hack has reported a similar association.¹

Finally, Dr Hack is concerned that our very-low-birth-weight infants' morbidity rates are improving at a time when others are documenting an opposite trend. She attributes this trend to greater survival rates of increasingly smaller and gestationally younger infants. While this may certainly be the case, the point is moot with respect to our study because the two groups of infants were of equivalent birth weights, gestational ages, and degree of illness. With degree of prematurity and illness between the two groups controlled for, we were able to show the significant improve-

ments in in-hospital growth and follow-up growth in the 1986 group.

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Lack of Associated Renal Anomalies in Familial Polythelia

Sir:—Recent articles have addressed the possible association of supernumerary nipples with renal anomalies. Kenney et al,¹ examining Israeli infants, and Mimouni et al,² examining American term neonates, demonstrated no associated renal anomalies with isolated supernumerary nipples. However, Hersh et al³ examined dysmorphic American children and Varsano et al⁴ examined Israeli children referred to an emergency department. They demonstrated associated renal anomalies in 11% and 23%, respectively, of those children with a supernumerary nipple. A recent study by Meggyessy and Mehes⁵ demonstrated renal abnormalities in 6 (8%) of 78 Hungarian patients hospitalized for illnesses unrelated to the urinary tract and healthy newborn infants.

A limited number of instances of familial polythelia have been reported. Hersh et al³ described two parent-child pairs with polythelia. Klinkerfuss⁶ found polymastia with inconsistent polythelia in five females in four generations.

Patient Report.—We report a case of an American family of four (father, aged 31 years; mother, aged 34 years; and two sons, aged 3 years and 5 years), all of whom were found on routine examination to have left-sided supernumerary nipple. In all of these patients, the supernumerary nipple was located along the embryologic milk line approximately 3 cm inferior to the normal nipple. There was no evidence of accessory breast tissue in any member of the family. Accessory areolae were present in the mother and father but not in the children. There was no additional family history of polythelia. All of the family members were without any history suggestive of underlying renal anomalies and, similarly, were without any evidence of additional congenital anomalies. The results of renal ultrasound procedures performed on all four family members were normal.

Comment.—This study of familial polythelia as a single congenital anomaly does not support an association with either clinically overt or occult renal anomalies.

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In Other AMA Journals

JAMA

Preterm Birth Prevention in a Rural Practice

B. P. Yawn, R. A. Yawn (*JAMA.* 1989;262:230-233)

Instructions for Authors

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4. Authors should be limited to six, all of whom have contributed to the study and manuscript preparation, are familiar with its substance, and are able to defend its conclusions.

5. The title page should give full names, degrees, and academic affiliations of all authors, address for request of reprints, and, if the manuscript was presented at a meeting, the organization, place, and exact date on which it was read.

6. Writing style should conform to proper English usage and syntax; consult the *American Medical Association Manual of Style*, available from Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202.

7. Abstract should be limited to 135 words or less.

8. Each table should be typed, with a title, on a separate sheet of paper, with each line, including headings, double-spaced. Continuations should be on a second sheet with all headings repeated.

9. Use *Système International* (SI) measurements throughout the manuscript.

10. Illustrations should be high-contrast, glossy prints, in quadruplicate, unmounted and untrimmed; lettering should be legible after reduction to column size. Figure number, name of first author, and arrow indicating “top” should be typed on a gummed label and affixed on the back of each illustration. Do not write directly on the print.

Magnification and stain should be provided for histologic sections. Full-color illustrations should be submitted as 35-mm, positive color transpar-

encies, mounted in cardboard and carefully packaged. Do not submit glass-mounted transparencies or color prints. Fee is \$400 for up to six square-finished color illustrations that fit on one page. A letter of intent to pay the fee must accompany submission.

All photographs in which there is a possibility of patient identification should be accompanied by a signed statement of consent from both parents (or guardians). Covering eyes to mask identity is not sufficient.

11. References should be listed in order of their appearance in the text, type double-spaced, and in AMA format. Please follow the exact order of information and punctuation in the examples below.

Journal Articles: Sell EJ, Gaines JA, Gluckman C, Williams E. Persistent fetal circulation: neurodevelopment outcome. *AJDC*. 1985;139:25-28.

Books: Krmpotic-Nemanic J, Kostovics I, Rudan P. Aging changes of the form and infrastructure of the external nose and its importance in rhinoplasty. In: Conly J, Dickinson JT, eds. *Elastic and Reconstructive Surgery of the Face and Neck*. New York, NY: Grune & Stratton; 1972:84-91.

Unpublished data, personal communications, or manuscripts “in preparation” or “submitted” should not be included in the list of references. Such material, if essential, may be incorporated in the body of the article.

Authors are responsible for the accuracy of the references.

12. Investigations involving human subjects require a specific statement in the “Methods” section that an appropriate institutional review board approved the project and/or that informed consent was obtained from both legal guardians and/or child, if appropriate.

13. Illustrations and tables from other publications should be suitably acknowledged, with written permission from publisher and author. Brief acknowledgements to specific contributors directly involved in the content of the manuscript may be placed at the end of the text, before the references. General acknowledgements will be deleted.

Step 3.—Special Departments.—Criteria for several special departments are given below.

1. **The Pediatric Forum.**—This is the place for comment, criticism, observations, and discussion of “issues of current concern and importance for children's health,” in addition to letters that comment on articles in previous issues of *AJDC*. The Editor reserves the right to conduct review of and to edit all submissions. THE READER SHOULD SUBMIT TRIPLE-SPACED COPY CLEARLY MARKED “FOR PUBLICATION” AND SIGNED BY ALL AUTHORS. REFERENCES, IF INCLUDED, SHOULD CONFORM TO THE USUAL AMA FORMAT. Copyright assignment, signed by all authors, must accompany the original submission.

2. **From Research to Relevance.**—PURPOSE: To focus on significant research that has a high probability of being translated into clinical usefulness.

3. **Educational Interventions.**—PURPOSE: To share information concerning any educational efforts in the broad field of pediatrics.

4. **Sports Medicine.**—PURPOSE: To provide current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention, diagnosis, and treatment of sports-related illnesses and injuries.

5. **Picture of the Month.**—Submissions should be sent directly to Murray Feingold, MD, National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135, and should conform to the format for original articles in terms of the text, references, and illustrations.

6. **Radiological Case of the Month.**—Submissions should be sent directly to Beverly P. Wood, MD, University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Submissions should conform to the format for original articles in terms of the text, references, and illustrations.

Author's Checklist

- ____ 1. Cover letter with name, address, and telephone number of corresponding author.
- ____ 2. Copyright transmittal, affirmation, and financial statements signed by ALL authors.
- ____ 3. Original typed manuscript plus three copies.
- ____ 4. Triple-spacing; double-spacing for tables and legends.
- ____ 5. Right margins UNJUSTIFIED.
- ____ 6. Title 75 characters or less.
- ____ 7. Abstract included.
- ____ 8. References in proper format, cited in numerical order.
- ____ 9. Four sets of illustrations.
- ____ 10. Four sets of legends for illustrations.
- ____ 11. Proper consent forms for patient photographs.
- ____ 12. Permission forms for illustrations previously published elsewhere.

Informed Consent and the Need for Delegalization

Dr Jeffrey R. Botkin,¹ in his article "Informed Consent for Lumbar Puncture," which appears in this issue of *AJDC*, provides physicians with an adequate legal definition of the concept of "informed consent." While I might, on technical grounds, have some objections to the way he describes the exceptions to the requirement for informed consent (see below), I think his articulation of the general principles is useful. Unfortunately, informed consent is not a concept with unvarying meaning. It is used in many

See also p 899.

different contexts and has many different meanings, depending on the court or commentator who is attempting to use the phrase. The two words, however, have generally accepted contextual meaning. Thus, "informed" means knowing, understanding, or aware. It does not mean the mere telling of fact, particularly when that information is not understood by the recipient. Thus, if I give the information in a language that is not understood by the recipient, the "telling" of the information does not constitute "informing" within the meaning of the phrase. The word "consent" means an act of free will not done under duress or force. Thus, to speak of informed consent in regard to complicated medical procedures that are not easily understood by a layman is a contradiction in terms, just as to talk about the informed consent of someone who is incapable of exercising free will is equally inappropriate. Informed consent is a great deal more than simply executing a legal document. Indeed, the phrase is so overused that it has lost all legally significant meaning.

From a medical point of view, informed consent is thought to be an important component of the resolution

of any number of medical/scientific problems. Several of these problems follow:

1. Providing medically routine care to competent adult patients. Here the consent is most often implied rather than expressed.

2. Providing medically routine but somewhat risky care to competent adult patients. Here the consent is apt to take the form of some intelligent discussion between the physician and patient but may still be undocumented.

3. Providing nonroutine and high-risk care to competent adults. Here the consent is apt to take some formal form that documents the disclosure of risk and the patient's consent.

4. Providing care of all of the above to incompetent adults and children. Here, the consent, in whatever form, must be obtained from a surrogate and is more likely to be documented.

5. Securing consent in experimental programs where the advance of scientific knowledge is the primary goal rather than the provision of care to individual patients. Here the documentation of consent is likely to be extensive and formal.

6. Withdrawing care from patients whose life is likely to be near its end. Here the consent must be very formal and well documented. This is particularly so when the consent is given in advance by way of such means as a living will or a durable power of attorney.

It is a mistake to believe that some vague concept of informed consent is the answer to all these very different problems. The vastness and scope of the literature on the topic (for example: Note, Appointing an Agent to Make Medical Treatment Choices, 84 Colum L Rev 985 [1984]; Macklin, Some Problems in Gaining Informed Consent From Psychiatric Patients, 31 Emory L J 345 [1982]; Bolland, The

Doctrines of Lack of Consent and Lack of Informed Consent in Medical Procedures in Louisiana, 45 Louisiana L Rev 1 [1984]; Gelfand, Living Will Statutes: The First Decade, 1987 Wisconsin L Rev 737 [1987]), the studies and commissions that have focused on the problems,² and the expressed concern of the physicians on the front line demonstrate the complexity of the concept. In short, it is clear that a recent legal commentator was straight on the mark when she noted the "polar viewpoints" that exist on the topic (Macklin, Some Problems in Gaining Informed Consent from Psychiatric Patients, 31 Emory L J 3456 [1982]).

The tragic story of Mary O'Conner highlights the issue. In her case last fall, the highest court in New York held that a hospital had the duty to force-feed an elderly, mentally incompetent patient who was unable to eat or drink without medical "assistance," in spite of the fact that her daughters, under oath, swore that their mother had "repeatedly stated that she did not want her life prolonged by artificial means if she was unable to care for herself." In so doing, the court established a standard that will be impossible to meet in the vast majority of cases. The court held that Mary O'Conner's consent had to be proved by "clear and convincing" evidence of a "settled and firm commitment" to natural death. Moreover, the court held that the trier of fact had to be convinced of the continued vitality of the commitment "as far as humanly possible." Judge Simons, in dissent, noted the inevitable consequences of the court's pronouncement:

... these new requirements will undoubtedly increase litigation in this area because medical and hospital personnel, fearful of civil and criminal liability, will hesitate to honor patients' wishes without judicial approval.

It seems clear that the O'Conner de-

cision will have effects far beyond its facts. It will be applied, rightly or wrongly, to many areas where informed consent is thought to be required. It may mark a reversal of the trend toward a notion of "reasonable consent," where common sense and human values hold sway over legal technicalities. Whatever the decision does, it will generate further confusion about the legal consequences of providing health care.

In an ideal and moral world, the decision to allow Mary O'Conner to die a peaceful and dignified death would not be a matter for the courts. Caregivers would not fear retribution for exercising moral and medical judgment. Families would be consulted and judgments made in privacy without the glare of judicial intervention. However, that world no longer exists. Today, medical technology and law have combined to create a world where morality and human privacy are rele-

gated to a minor, if not inconsequential, role.

To restore the primacy of human values requires bold action by the medical and legal professionals who must live day to day with consequences of overlegalization and judicial intervention in private decision making. The legislature has the power to largely remove the courts from this process and I believe it should do so. We need to "delegalize" the notion of informed consent and provide by statute for a sphere of protected decision making, where patients and physicians can exercise judgment about health care decisions that will not be second guessed. Such an undertaking would bring great benefits to all concerned and it is, in my estimation, an achievable goal. It will require hard choices and the undertaking of risk. The end result, however, would be a more humane and functional process for the making of health care deci-

sions.

By statute, we can restore the primacy of individual decision making and the morality of private choice. If we continue with the case-by-case decision-making process that we have followed for the last few decades, we will sink ever further into a morass of legalisms that ill serve the needs of health care professionals, patients, and society.

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Chronic Sinusitis

The Disease of All Ages

Sinusitis is one of the most frequently overlooked and poorly understood diseases of childhood. There is a lack of information regarding criteria for diagnosis and the most effective method of management of sinusi-

See also p 938.

tis in children. Controversy exists regarding whether a sinus cavity is infected, how to diagnose sinusitis, and what the best treatment choice and duration is. The article by Tinkelman and Silk¹ in this issue of *AJDC* has prompted this editorial to bring

the pediatrician up to date regarding these issues. I will limit my remarks to chronic sinusitis, that is, compatible symptoms that have been present for at least 3 weeks. (Some experts in the field would shorten this time to 10 days.^{2,3})

The nasal sinuses are four paired structures: the maxillary, ethmoidal, sphenoidal, and frontal sinuses that develop as evaginations of the mucous membranes of the nasal meatuses. The origin of the ethmoid and maxillary sinuses is apparent by the third to fifth month of intrauterine life, and air is apparent in these sinuses shortly

after birth. Thus, sinusitis *can occur at any age and is not limited* to children over 5 years of age. The frontal sinuses appear radiographically by the seventh year, the sphenoids by the ninth year. The sinuses seem to function as organs to warm and humidify inhaled air, secrete mucus, capture foreign airborne particles and remove them from inspired air, increase olfactory sensitivity, impart resonance to the voice, and act as shock absorbers.

The sinuses rely on mucociliary clearance for drainage. The blanket of mucus helps in defense against sinus infections. Mucociliary action directs

the mucus and its trapping to the sinus ostia that opens into the nose. Obstruction in the region of the osteomeatal complex can produce obstruction and subsequent disruption of the involved sinus. Ciliary and mucous blanket function is disturbed and local resistance factors are diminished, resulting in accumulation of mucous secretions and inflammation with subsequent bacterial contamination.

The major factors implicated in the initiation of this process are viral upper respiratory tract infection and allergic rhinitis. Other factors include swimming, abuse of topical nasal decongestants, immune deficiency (especially selective IgA deficiency), and structural abnormalities. About 40% of children with chronic sinusitis have allergic rhinitis.

The diagnosis of chronic sinusitis is made by medical history and physical examination and is supported by roentgenographic findings, with the medical history usually providing a strong index of suspicion. The predominant symptom of chronic sinusitis is night and day coughing; there also may be nasal obstruction, nasal discharge, postnasal drip, sore throat, and fetor oris. Nasal symptoms may be minimal or absent. Fever and headache are uncommon. If the patient also has asthma, it is often harder to control when there is concomitant chronic sinusitis, and in these patients, sinusitis may be the only trigger of asthma. In this case, treating the sinusitis will decrease or eliminate the asthma.

The cough usually begins shortly after lying down at night, lasting for 1 to 2 hours and then resuming early in the morning and sometimes (10%, in my experience) it is associated with vomiting. Up to 60% of children with chronic sinusitis will have associated middle-ear disease. Fatigue, malaise, decreased appetite, and weight loss are associated complaints. Parents usually complain of a "cold" that never went away or a cough that is hard to control.

Physical examination reveals rhinorrhea, a red boggy nasal mucosa, postnasal drip, erythema, and cobblestoning in the posterior pharynx, with swelling of the lateral lymphoid

tissue. The nasal drainage can vary; it may be absent or diffuse, the color may be clear, yellow, or green, and the consistency may vary from thin to thick. Therefore, do not rely on the color to make a diagnosis of sinusitis.

Diagnostic aids commonly used are cytologic examination of nasal secretions, roentgenography, transillumination, and ultrasonography. Because nasal cultures are contaminated with other organisms, they do not give an adequate picture of the organisms responsible for sinusitis and therefore should not be done. The peripheral white blood cell count and the differential cell count as well as the erythrocyte sedimentation rate are of value only in the child with acute sinusitis.

Fresh nasal secretions with a large number of polymorphonuclear cells, especially with intracellular bacteria, is a frequent finding. While these cells may be seen during a viral upper respiratory tract infection, their presence in large numbers in a profuse rhinorrhea of several weeks' duration suggests sinusitis. In the child with allergic rhinitis, this nasal smear will have polymorphonuclear cells and not eosinophils. An abnormal nasal smear finding is sensitive but not a very specific predictor of sinusitis in the allergic child.

A good roentgenogram is the most reliable adjunct in the clinical diagnosis of sinusitis. Persistent chronic obstruction of the sinuses is usually associated with infection in the maxillary sinuses, even if the infection begins in the ethmoids. There are four standard views used in the roentgenographic evaluation of the paranasal sinuses: occipitomeatal (Waters), occiput frontal (Caldwell), lateral, and submentovertical. The Waters view is usually adequate, since this provides the best view of the maxillary sinuses. Diffuse opacification, mucosal thickening greater than 50% of the antrum (usually 4 to 6 mm or more), or an air-fluid level is considered diagnostic of a bacterial infection. Although there may be active infection with less prominent mucous membrane thickening, the correlation with culture evidence for infection and/or response to antimicrobial drugs is weaker. In these instances, the total clinical picture and

clinical judgment should dictate therapy. Allergic or vasomotor rhinitis do not result in significant sinus mucosal thickening. In my experience and the experience of others, sinus roentgenograms are not helpful in the child under 1 year of age.⁴

A-mode ultrasound, primarily useful for the detection of retained secretion and not mucosal thickening, is not sensitive and specific enough in children to be a helpful diagnostic tool. Transillumination may be a useful screening tool in adults but is not useful in detecting sinusitis in children. The role of computed tomographic scanning and magnetic resonance imaging has not been evaluated in children. Crying does not result in abnormal roentgenograms.

Most studies on the bacterial causes of sinusitis have involved adults. In acute sinusitis in children, *Streptococcus pneumoniae*, nontypeable *Haemophilus influenzae*, and *Branhamella catarrhalis* are the major organisms. Studies of chronic sinusitis in children are limited. Brook⁵ (40 patients) demonstrated anaerobic organisms, including *Bacterioides* species, α -hemolytic streptococci, *Staphylococcus aureus*, and *Haemophilus* species, while a study of 8 children⁶ revealed *B catarrhalis*, *H influenzae*, and *S pneumoniae*.

Tinkelman and Silk demonstrated that 22 of 35 children with chronic sinusitis had positive bacterial cultures of the sinus aspirate, with 19 of the 22 children being under the age of 5 years. The most common organisms isolated were *H influenzae*, *S pneumococcus*, and *B catarrhalis*. They reported that 5 of 8 *S pneumococci* organisms recovered were relatively resistant to penicillin. Anaerobic organisms were not isolated. There are several problems with their study, including its retrospective design, the lack of clinical data on the children (ie, truly allergic vs nonallergic), and the involvement of four hospitals indicating the likelihood that techniques may have varied from place to place and time to time. In particular, how much credence can we place in the statement that all air was expelled from the syringes and that all cultures were set up within 30 minutes of collection?

Anaerobic transport setups could have been better, and most laboratories would have incubated the chocolate agar under 10% carbon dioxide. They should have used a nonselective anaerobic medium. These points and prior therapy could have accounted for the lack of recovery of anaerobes. All of the patients were receiving antibiotic therapy (and repeated courses) at the time of specimen collection; this would limit the number of positive cultures and account for the relatively resistant organisms. Apparently specimens were only taken during the maxillary punctures, not during the surgical procedures; the latter would have provided better specimens. I would like to know why so many antral windows were done since this is an uncommon procedure in children, especially during the first surgical intervention. In addition, minimum inhibitory concentrations with penicillin and the pneumococci would have been most helpful.

We recently completed a study of 12 children (3 to 9 years of age) with allergic rhinitis complicated by chronic maxillary sinusitis.⁷ Sinus aspiration/irrigation culture results revealed a pure growth of *B. catarrhalis* in 5 of 12 patients, four of which were β -lactamase positive. The cultures of 4 patients yielded mixed species (one mixed *Branhamella* and streptococcal species and three mixed streptococcal species). Three patients' sinus cultures yielded no organisms. The study demonstrated clinical improvement even in patients with negative cultures, ie, just evacuating the maxillary sinus was exceedingly helpful.

The management of chronic sinusitis must be directed to the known bacteriology of this disease. More studies are necessary. However, my recommendation would be a trial of an antimicrobial agent(s) (amoxicillin with clavulanic acid), an oral cephalosporin (cefuroxime or cefaclor), or erythromycin and a sulfonamide (given together or as full separate daily doses) for a period of 2 or 3 weeks. If there is no clinical response, then another antimicrobial agent from this group is given for 3 more weeks. Clinical response usually occurs within 5 days, with decreased cough, less rhinor-

rrhea, and improved well-being. If clinical and laboratory response is inadequate, I strongly urge consideration of mechanical sinus aspiration and lavage with appropriate culture and antimicrobial therapy appropriate for the organism recovered. The role of endoscopic surgery and the treatment of the osteomeatal complex at this stage of a child's chronic sinusitis needs to be evaluated further. The initial reports suggested that the endoscopic approach might be more effective than just the plain mechanical aspiration and lavage of the sinuses. I do not repeat sinus roentgenograms if there is a clinical response; I usually do them again if (1) I'm considering surgical intervention, (2) the child has had frequent clinical sinusitis with brief "well" periods while not receiving antibiotic therapy, or (3) the asthma (if present) continues to be a management problem.

I do not recommend an antral window unless the antral lavage needs to be repeated within a 6-month period. My experience is that less than 2% of children need to have repeated surgical intervention in so short a time. Approximately 10% of my patients will need another lavage. These children usually have IgA deficiency or poorly controlled allergic rhinitis. Adenoidectomy is of uncertain benefit in the prevention or treatment of chronic sinusitis. However, if postnasal obstruction is present, adenoidectomy will improve the nasal airway. Some children will have bacterial infection of the adenoids, the source of chronic or repeated airway infection.

The role of antihistamines, decongestants, nasal cromolyn sodium, and nasal corticosteroids has not been evaluated in children with chronic sinusitis. The nonallergic child, without a predisposing factor, with recurrent sinusitis sometimes benefits from the antiinflammatory effects of either or both topical medications. The child with allergic rhinitis needs to have the allergic disorder treated properly, or the sinusitis will become recurrent. Such management should include environmental control, the avoidance of cigarette smoke and swimming, medication, and, at times, immunotherapy. I have been impressed with topical

therapy (cromolyn sodium or corticosteroids) in such children and it should be continued for a minimum of 6 months. I sometimes combine medications and have initiated one or both therapies in children under 5 years of age.

My colleagues and I are impressed by the number of sufferers of chronic rhinitis we see whose presentation is bacterial sinusitis. Many of these children have had recurrent chronic middle-ear disease that does not improve until the sinus disease is improved or cured. We have seen many children under the age of 2 years with this problem. The report by Timan and Silk also has demonstrated this. We are impressed with the number of children with asthma who have difficult-to-control airways and do not respond to proper management including corticosteroid therapy, the underlying sinusitis is recognized and treated.

Now that sinusitis is a recognized and acceptable disorder in children of all ages, it is important to study true incidence, modes of therapy, and reasons it occurs.

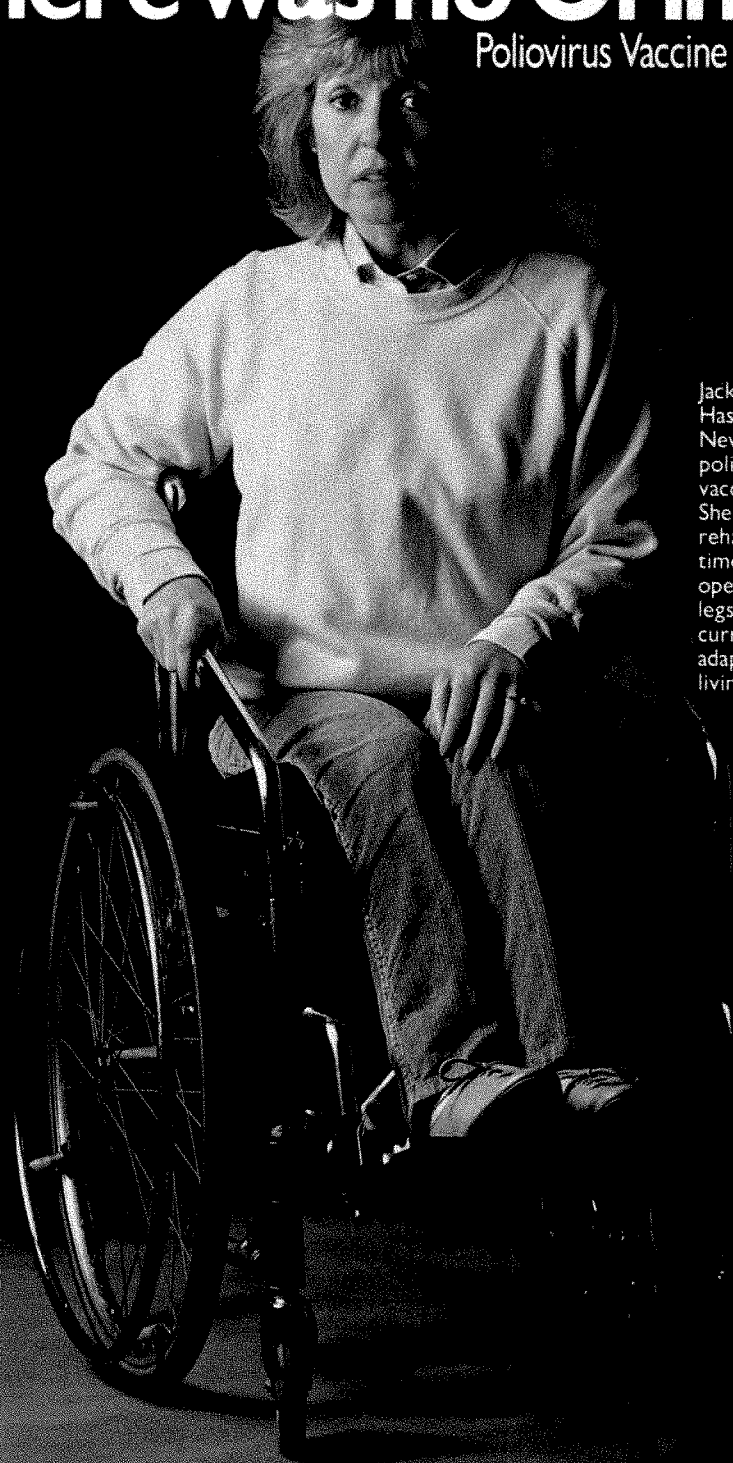
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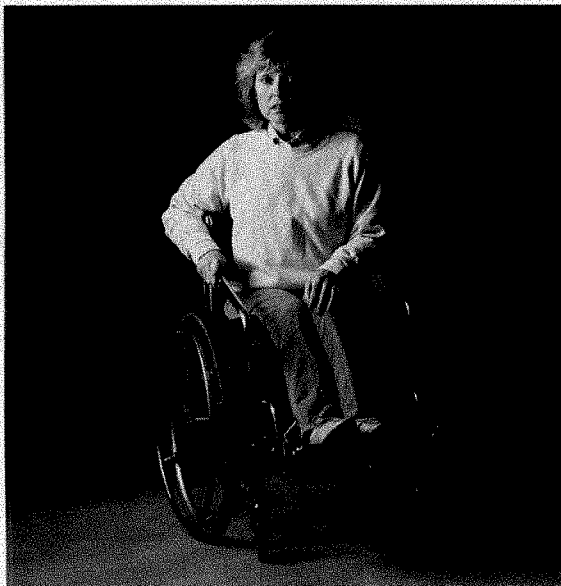
Jackie DiLorenzo of Hastings-on-Hudson, New York, contracted polio in 1950, before a vaccine became available. She spent ten years in rehabilitation, during which time she underwent nine operations on her spine, legs and feet. Jackie currently lives in a house adapted for wheelchair living.



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WARNINGS: Under no circumstances should this vaccine be administered parenterally.

Administration of the vaccine should be postponed or avoided in those experiencing any acute illness and in those with any advanced debilitated condition or persistent vomiting or diarrhea.

Other viruses (including poliovirus and other enteroviruses) may interfere with the desired response to this vaccine, since their presence in the intestinal tract may interfere with the replication of the attenuated strains of poliovirus in the vaccine.

PRECAUTIONS: It would seem prudent not to administer trivalent oral poliovaccine (OPV) shortly after Immune Globulin (IG) unless such a procedure is unavoidable. For example, with unexpected travel to or contact with epidemic areas or endemic areas. If OPV is given with or shortly after IG, the dose probably should be repeated after three months if immunization is still indicated.

The vaccine is not effective in modifying or preventing cases of existing and/or incubating poliomyelitis.

Use in Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Poliovirus vaccine live oral trivalent. It is also not known whether OPV can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Although there is no convincing evidence documenting adverse effects of either OPV or IPV on the developing fetus or pregnant woman, it is prudent on theoretical grounds to avoid vaccinating pregnant women. However, if immediate protection against poliomyelitis is needed, OPV is recommended. (See CONTRAINDICATIONS and ADVERSE REACTIONS.)

ADVERSE REACTIONS: Paralytic disease following the ingestion of live poliovirus vaccines has been, on rare occasion, reported in individuals receiving the vaccine (see, for example, CONTRAINDICATIONS), and in persons who were in close contact with vaccinees. The vaccine viruses are shed in the vaccinee's stools for at least six to eight weeks as well as via the pharyngeal route. Most reports of paralytic disease following ingestion of the vaccine or contact with a recent vaccinee are based on epidemiological analysis and temporal association between vaccination or contact and the onset of symptoms. Most authorities believe that a causal relationship exists. Prior to administration of the vaccine, the attending physician should warn or specifically direct personnel acting under his authority to convey the warnings to the vaccinee, parent, guardian, or other responsible person of the possibility of vaccine-associated paralysis, particularly to susceptible family members and other close personal contacts. The Centers for Disease Control report that during 1972 to 1983, approximately 278.8 million OPV doses were distributed in the United States. During this same period, 87 vaccine-associated cases in apparently immunologically normal individuals were reported. Thirty-two occurred among vaccine recipients (one case per 8.7 million OPV doses distributed), and 55 cases occurred among household and nonhousehold contacts of vaccinees (1 case per 5.1 million doses distributed). Sixteen other vaccine-associated cases have been reported in persons (recipients or contacts) with immune deficiency conditions.

Because the number of susceptible vaccine recipients or contacts of recipients is not known, the true risk of vaccine-associated poliomyelitis is impossible to determine precisely.

When the attenuated vaccine strains are to be introduced into a household with adults who have not been adequately vaccinated or whose immune status cannot be determined, the risk of vaccine-associated paralysis can be reduced by giving these adults one dose of IPV per month for three months before the children receive Poliovirus vaccine live oral trivalent ORIMUNE. The children may receive the first dose of ORIMUNE at the same visit that the adult receives the third dose of IPV. The CDC reports that no paralytic reactions to IPV are known to have occurred since the 1955 cluster of poliomyelitis cases caused by vaccine that contained live polioviruses that had escaped inactivation.

The ACIP states: "Because of the overriding importance of ensuring prompt and complete immunization of the child and the extreme rarity of OPV-associated disease in contacts, the Committee recommends the administration of OPV to a child regardless of the poliovirus-vaccine status of adult household contacts. This is the usual practice in the United States. The responsible adult should be informed of the small risk involved. An acceptable alternative, if there is a strong assurance that ultimate, full immunization of the child will not be jeopardized or unduly delayed, is to immunize adults according to the schedule outlined above before giving OPV to the child."

The ACIP has concluded that "Oral polio vaccine remains the vaccine of choice for primary immunization of children."

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**Lets kids be kids
12 hours long**

BRIEF SUMMARY

AVIST®

(clemastine fumarate) SYRUP 0.5 mg/5 ml
 (present as clemastine fumarate 0.67 mg/5 ml)

INDICATIONS AND USAGE

Avist® (clemastine fumarate) Syrup is indicated for the relief of symptoms associated with allergic rhinitis such as sneezing, rhinorrhea, pruritus and lacrimation. Tavist® (clemastine fumarate) Syrup is indicated for use in pediatric populations (ages 6 years through 12) and adults (see **DOSAGE AND ADMINISTRATION**).

It should be noted that Tavist® (clemastine fumarate) is indicated for the relief of mild, uncomplicated allergic skin manifestations of urticaria and angioedema at the 2 mg dosage level only.

CONTRAINDICATIONS

Antihistamines are contraindicated in patients hypersensitive to the drug or to other antihistamines of similar chemical structure (see **PRECAUTIONS — Drug Interactions** in a complete package insert).

Antihistamines should not be used in newborn or premature infants. Because of the higher risk of antihistamines for infants generally and for newborns and premature infants in particular, antihistamine therapy is contraindicated in nursing mothers (see **PRECAUTIONS — Nursing Mothers** in a complete package insert).

WARNINGS

Antihistamines should be used with considerable caution in patients with: narrow angle glaucoma, stenosing peptic ulcer, prostatic hyperplasia, symptomatic prostatic hypertrophy, and bladder neck obstruction.

Use with CNS Depressants: Tavist® (clemastine fumarate) has additive effects with alcohol and other CNS depressants (sedatives, tranquilizers, etc.).

Use in Activities Requiring Mental Alertness: Patients should be warned about engaging in activities requiring mental alertness such as driving a car or operating appliances, machinery, etc.

Use in the Elderly (approximately 60 years or older): Antihistamines are more likely to cause dizziness, sedation, and potentiation in elderly patients.

ADVERSE REACTIONS

The most frequent adverse reactions are underlined:

Nervous System: Sedation, sleepiness, dizziness, disturbed coordination, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesia, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis, hysteria, neuritis, convulsions.

Gastrointestinal System: Epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.

Respiratory System: Thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness.

Cardiovascular System: Hypotension, headache, palpitations, tachycardia, extrasystoles.

Hematologic System: Hemolytic anemia, thrombocytopenia, granulocytosis.

Genitourinary System: Urinary frequency, difficult urination, urinary retention, early menses.

General: Urticaria, drug rash, anaphylactic shock, photosensitivity, excessive perspiration, chills, dryness of mouth, nose and throat.

DOSAGE AND ADMINISTRATION

DOSAGE SHOULD BE INDIVIDUALIZED ACCORDING TO THE NEEDS AND RESPONSE OF THE PATIENT.

Pediatric: Children aged 6 to 12 years

For Symptoms of Allergic Rhinitis — The starting dose is 1 teaspoonful (0.5 mg clemastine) twice daily. Since single doses up to 2.25 mg clemastine were well tolerated by this age group, dosage may be increased as required, but not to exceed 3 teaspoonsful daily (3 mg clemastine).

For Urticaria and Angioedema — The starting dose is 2 teaspoonsful (1 mg clemastine) twice daily, not to exceed 6 teaspoonsful daily (3 mg clemastine).

Adults and Children 12 Years and Over

For Symptoms of Allergic Rhinitis — The starting dose is 1 teaspoonful (1 mg clemastine) twice daily. Dosage may be increased as required, but not to exceed 12 teaspoonsful daily (3 mg clemastine).

For Urticaria and Angioedema — The starting dose is 4 teaspoonsful (2 mg clemastine) twice daily, not to exceed 12 teaspoonsful daily (6 mg clemastine).

HOW SUPPLIED

Avist® (clemastine fumarate) Syrup

Clemastine 0.5 mg/5 ml (present as clemastine fumarate 0.67 mg/5 ml). A clear, colorless liquid with a citrus flavor, in 4 fl. oz. bottle (NDC 0078-0222-31).

[TAS-Z3 APRIL 1, 1986]

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PEDIATRICIAN:

The Department of Pediatrics, University of California, Davis, is seeking an established academic general pediatrician with proven excellence in clinical care and education of students and housestaff plus proven productivity in clinical research. Major responsibility will be in the ambulatory setting and in administering the education programs of the department. Submit CV and the names and addresses of five references to Dennis M. Styne, M.D., Chair, Department of Pediatrics-3104 PCC, 4301 X Street, Sacramento CA 95817. The University of California is an affirmative action/equal opportunity employer. All Applications Must Be Received No Later Than 10/30/89 To Be Considered.

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Rubella and Congenital Rubella Syndrome—United States, 1985–1988

RUBELLA

A provisional total of 221 cases of rubella was reported in the United States in 1988 (0.1 cases per 100,000 population), the lowest since rubella became a nationally notifiable disease in 1966. The incidence of rubella has declined by more than 99% since 1969, the year rubella vaccine was licensed.

In 1987, the last year for which complete data are available, 20 of 52 reporting areas (which comprise the 50 states, District of Columbia, and New York City [NYC]) reported no rubella cases, compared with 18 reporting areas in 1986 and 14 in 1985. The reported age-specific incidence rates of rubella declined for all age groups during these 3 years.

Long-term trends of rubella incidence among specific age groups can be assessed by comparing recent data from the total United States with those from three areas for which age-specific data were available before 1975—Illinois, Massachusetts, and NYC. The reported incidence rates for 1985–1987 have declined by greater than or equal to 95% for all age groups, with the greatest decreases occurring among persons less than 20 years of age.

CONGENITAL RUBELLA SYNDROME

Data on congenital rubella syndrome (CRS) are available from reports submitted weekly to the MMWR and from the National Congenital Rubella Syndrome Registry (NCRSR) maintained at the Division of Immunization, Center for Prevention Services, CDC. The MMWR CRS reports are case counts with no accompanying data and are tabulated by year of report. The NCRSR contains clinical and laboratory information on cases of CRS that are reported by state and local health departments. The NCRSR cases are monitored by year of patient's birth and are classified into six clinical categories,¹ the most specific of which are "CRS-confirmed"

(i.e., cases with both congenital anomalies and laboratory evidence of rubella infection) and "CRS-compatible" (i.e., cases that satisfy selected clinical criteria without laboratory confirmation). Beginning in 1984, information was routinely collected to evaluate whether a CRS case was "indigenous" or "imported."* Since the NCRSR cases are classified by year of patient's birth, data are considered provisional for any given year; delays in diagnosis and/or reporting may result in the updating of figures. This summary updates previous reports on surveillance of CRS in the United States.¹

For infants born in 1987, six CRS cases were reported to the NCRSR, of which three were considered indigenous. All three were confirmed CRS cases, and one of them occurred in a mother who had had at least one previous pregnancy. Only one CRS case has been reported thus far for 1988. Recent declines in rates of CRS recorded by NCRSR have paralleled the decline in overall rubella incidence and, more specifically, in the incidence for persons greater than or equal to 15 years of age. During 1970–1987, the reported rate of rubella among persons in this age group declined 97%, from 2.3 to 0.1 cases/100,000 population. In 1970, 67 CRS cases occurred (1.80/100,000 live births), and three have been reported as of March 22, 1989, for 1987 (0.08/100,000 live births), representing a 96% decline. This downward trend was interrupted in 1986, when 12 CRS cases were reported.² In that year, eight of these cases were reported to the NYC Department of Health 8–10 months after the peak of a rubella outbreak in NYC.³

Reported by: Surveillance, Investigations, and Research Br, Div of Immunization, Center for Prevention Svcs, CDC (MMWR vol 38, No. 11).

CDC Editorial Note: As part of the 1990 health objectives for the nation, the Public Health Service set a goal to reduce the number of rubella cases to less than 1000 and to reduce CRS to

less than 10 cases annually.⁴ The former goal was achieved for the first time in 1983, when 970 rubella cases were reported.⁵ Although the goal for CRS has also been reached, unacceptable morbidity is still occurring. The primary aim of rubella vaccination programs is to prevent congenital rubella infection, which can result in miscarriages, abortions, stillbirths, and CRS in infants. When rubella vaccine was licensed in 1969, the United States adopted a policy of universal immunization of children of both sexes. The focus of this rubella vaccination strategy was to control rubella in preschool-aged and young school-aged children, the primary sources of rubella transmission. This strategy was designed primarily to reduce and interrupt circulation of the virus, thereby reducing the risk of exposure to susceptible pregnant women. Also, vaccinated children would be protected immediately, and their immunity was expected to persist at least through their childbearing years.⁶ Secondary emphasis was placed on vaccinating susceptible adolescents and adults, especially women.

The success of the rubella control program is apparent. In 1966–1987, the reported incidence rates of CRS and of rubella among persons greater than or equal to 15 years of age declined in parallel by 95%–96% to all-time low levels. Meanwhile, incidence rates of rubella in children less than 15 years of age have continued their downward trend. As the highly immune cohorts of young children enter the childbearing years, CRS should disappear from this country.

However, concern continues despite the dramatic success of the U.S. rubella immunization program. In 1987, 48% of reported rubella cases were in persons greater than or equal to 15 years of age (32% of all cases were in persons 15–29 years of age). Most serologic surveys of various postpubertal populations carried out during the 1970s and early 1980s found rates of rubella susceptibility comparable to the prevaccine years: 10%–20% of persons still lacked serologic evidence of immunity to rubella.^{7–9} Updated population-based serologic surveys are needed to fully characterize the magnitude and extent of risk for this adolescent and young adult population. The NYC experience during 1985–1986^{2,3} and several recent college outbreaks¹⁰ highlight the possible risk of disease in postpubertal women. The continued occurrence of rubella in childbearing-aged populations sug-

gests that potentially preventable cases of CRS may continue to occur during the next 10–30 years. Such concerns led CDC to announce an initiative in February 1985 to hasten elimination of rubella and CRS by targeting susceptible childbearing-aged populations for vaccination.¹¹

In addition, the reported figure for CRS cases is believed to underestimate the actual total, perhaps capturing only 10% of the actual total.¹² The NCRSR is a passive reporting system that, by its nature, results in under-reporting of actual disease incidence and selective reporting of infants with severe and obvious CRS recognized and reported early in life. The limitations of current CRS surveillance underscore the need for all specialists who treat children with congenital anomalies compatible with CRS to continue to consider it in the differential diagnosis and to report all suspected cases to their state health departments.

As with other adult immunizations, creative approaches are necessary to enhance rubella immunization levels in the childbearing-aged population. Adopting and enforcing comprehensive kindergarten through 12th grade school immunization laws (especially for postpubertal elementary and secondary school students) and requiring proof of immunity to rubella as a condition for college entry can minimize the risk of rubella outbreaks in these populations.¹³ Another way to reach

susceptible postpubertal women is to offer rubella vaccine at any encounter with the health-care system. After excluding patients who say they may be pregnant and counseling about the advisability to avoid conception for 3 months after vaccination, practitioners should not hesitate to vaccinate childbearing-aged women against rubella. No CRS-like defects have been detected in 212 infants born to susceptible mothers inadvertently vaccinated with RA27/3 live rubella virus vaccine during pregnancy (14; CDC, unpublished data). NCRSR surveillance data indicate that one third to one half of mothers delivering CRS infants had had a previous live birth, suggesting that both postpartum vaccination and use of rubella vaccine in family-planning clinics could have an important impact on the overall occurrence of reported CRS. Physicians and other health-care personnel should offer rubella vaccine whenever they encounter a potentially susceptible woman lacking contraindications for vaccination. Susceptible persons identified through preemployment, premarital, or prenatal screening should be offered vaccine at follow-up visits.

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*Based on definitions approved by the Council of State and Territorial Epidemiologists, an imported case of CRS is defined as CRS in a U.S. or non-U.S. citizen whose mother was outside the United States during her presumed exposure to rubella. If the timing of exposure to rubella cannot be determined, the mother must have been outside the United States throughout the 21 days before conception and the first 20 weeks of her pregnancy.

Reye Syndrome Surveillance—United States, 1987 and 1988

FOR THE 1987 and 1988 surveillance years, 36 and 20 cases, respectively, of Reye syndrome (RS) were reported to the National Reye Syndrome Surveillance System. These years have the lowest number of cases reported since continuous national surveillance was established in December 1976. For both years, approximately 80% of reported patients had an antecedent illness within 3 weeks before onset of vomiting or neurologic symptoms. Eighteen RS patients in 1987 and nine in 1988 had respiratory illnesses; seven and four had varicella; three and two had diarrhea without respiratory symptoms. In both years, approximately 50% of cases occurred in January, February, and March—the peak months for respiratory viral infections, including varicella and influenza (type A[H1N1] in 1987 and type

A[H3N2] in 1988).

In 1987, 17 (47%) of the 36 reported RS patients and, in 1988, 16 (80%) of the 20 patients were female; 33 (92%) and 19 (95%), respectively, were white, two (6%) and one (5%) were black, and one patient (3%) in 1987 was Asian. Seventeen patients each year were greater than or equal to 5 years old, representing a 75% decline in the number of cases in this age group from 1986. Nineteen reported patients in 1987 and three in 1988 were less than 5 years old, representing a 42% and a 91% decline, respectively, in this age group from 1986.

Approximately 75% of patients in both 1987 and 1988 were admitted to hospitals in precomatose stages of RS—stages 0, 1, or 2. In each year, stage 2 was the classification for the largest number of patients upon ad-

mission (47% and 55%, respectively), followed by stage 1 for 1987 (31%) and stages 0, 1, and 3 (10% each) for 1988. In 1987, the most severe phases of illness after hospitalization were stage 1 (25%), stage 2 (8%), stage 3 (8%), stage 4 (11%), and stage 5 (30%). Eleven percent of patients received treatment that precluded classification (i.e., they had received anesthetic or paralyzing agents in their treatment); the most severe stage was not reported for 7%. In 1988, 25% reached stage 1 only; 5% reached stage 2, 20% reached stage 3, 20% reached stage 5, and 30% received treatment that precluded classification.

Reported by: Epidemiology Office, Div of Vira and Rickettsial Diseases, Center for Infectious Diseases, CDC (*MMWR* vol 38, No. 18).



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PEDICULICIDAL/OVICIDAL ACTIVITIES: *In vitro* data indicate that permethrin has pediculicidal and ovicidal activity against *Pediculus humanus var. capitis*. The high cure rate (97-99%) of Nix in patients with head lice demonstrated at 14 days following a single application is attributable to a combination of its pediculicidal and ovicidal activities and its residual persistence on the hair which may also prevent reinfestation.

INDICATIONS AND USAGE: Nix is indicated for the single-application treatment of infestation with *Pediculus humanus var. capitis* (the head louse) and its nits (eggs). Retreatment for recurrences is required in less than 1% of patients since the ovicidal activity may be supplemented by residual persistence in the hair. If live lice are observed after at least seven days following the initial application, a second application can be given.

CONTRAINDICATIONS: Nix is contraindicated in patients with known hypersensitivity to any of its components, to any synthetic pyrethroid or pyrethrin, or to chrysanthemums.

WARNING: If hypersensitivity to Nix occurs, discontinue use.

PRECAUTIONS:

General: Head lice infestation is often accompanied by pruritus, erythema, and edema. Treatment with Nix may temporarily exacerbate these conditions.

Information for Patients: Patients with head lice should be advised that itching, redness, or swelling of the scalp may occur after application of Nix. If irritation persists, they should consult their physician. Nix is not irritating to the eyes; however, patients should be advised to avoid contact with eyes during application and to flush with water immediately if Nix gets in the eyes. In order to prevent accidental ingestion by children, the remaining contents of Nix should be discarded after use.

Combing of nits following treatment with Nix is not necessary for effective treatment. However, patients may do so for cosmetic or other reasons. The nits are easily combed from the hair treated with Nix after drying.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Six carcinogenicity bioassays were evaluated with permethrin, three each in rats and mice. No tumorigenicity was seen in the rat studies. However, species-specific increases in pulmonary adenomas, a common benign tumor of mice of high spontaneous background incidence, were seen in the three mouse studies. In one of these studies there was an increased incidence of pulmonary alveolar-cell carcinomas and benign liver adenomas only in female mice when permethrin was given in their food at a concentration of 5000 ppm. Mutagenicity assays, which give useful correlative data for interpreting results from carcinogenicity bioassays in rodents, were negative. Permethrin showed no evidence of mutagenic potential in a battery of *in vitro* and *in vivo* genetic toxicity studies. Permethrin did not have any adverse effect on reproductive function at a dose of 180 mg/kg/day orally in a three-generation rat study.

Pregnancy: Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits (200-400 mg/kg/day orally) and have revealed no evidence of impaired fertility or harm to the fetus due to permethrin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the evidence for tumorigenic potential of permethrin in animal studies, consideration should be given to discontinuing nursing temporarily or withholding the drug while the mother is nursing.

Pediatric Use: Nix is safe and effective in children two years of age and older. Safety and effectiveness in children less than two years of age have not been established.

ADVERSE REACTIONS: The most frequent adverse reaction to Nix is pruritus. This is usually a consequence of head lice infestation itself, but may be temporarily aggravated following treatment with Nix. 5.9% of patients in clinical studies experienced mild temporary itching; 3.4% experienced mild transient burning/stinging, tingling, numbness, or scalp discomfort; and 2.1% experienced mild transient erythema, edema, or rash of the scalp.

DOSAGE AND ADMINISTRATION:

Adults and Children: Nix is intended for use after the hair has been washed with shampoo, rinsed with water and towel dried. Apply a sufficient volume of Nix to saturate the hair and scalp (especially behind the ears and on nape of the neck). Nix should remain on the hair for 10 minutes before being rinsed off with water. A single treatment is sufficient to eliminate head lice infestation. Combing of nits is not required for therapeutic efficacy, but may be done for cosmetic reasons or to meet school 'no nit' policies. A nit comb is provided.

SHAKE WELL BEFORE USING.

HOW SUPPLIED: Nix (Permethrin) 1% (wt./wt.) Creme Rinse is supplied in plastic squeeze bottles that contain 2 fl. oz. weighing 56 g. (NDC-0081-0780-81)

Store at 15°-25°C (59°-77°F).

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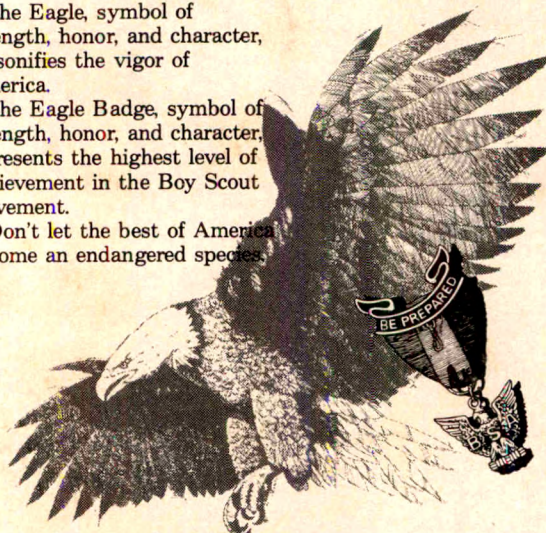
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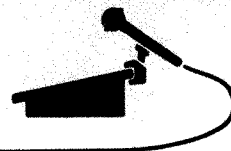
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The Editorial Board Speaks . . .

Peggy C. Ferry, MD



Dr Ferry is completing sabbatical leave from her position as professor of pediatrics and neurology at the University of Arizona, Tucson. She was a visiting scientist, Developmental Neurology Branch, Division of Convulsive, Developmental, and Neuromuscular Disorders, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Md. Her major project this year was to conduct a survey of the neurological complications and consequences of cardiac surgical procedures in infants and children. Her original work appeared in *AJDC* (1987;141:309-312). In addition, Peggy continues as our book review editor, and her long love of books stands her in good stead in this role for *AJDC*. Peggy has also published recently a tribute to Amos Christie and a commentary on the confusion attendant on new brain-death guidelines in children. She also has served as guest faculty for the Children's Hospital and Health Center in San Diego, Calif, the University of California at San Francisco, and for several of the American Academy of Pediatrics continuing education courses. She just completed a 5-year term as the neurology representative on the Committee on Scientific Meetings of the American Academy of Pediatrics.

ACUTE REMUNERATIVE NEUROLOGY

The journal ads are bright and colorful. They describe EEG and EMG equipment with trendy, catchy headings:

- "A New Dimension in Neurodiagnostics"
- "The Leading Light in EMG/Evoked Responses"
- "Now Sleep Labs Can Make House Calls"
- "Evoked Potential Technology at Your Fingertips (Learn in the morning, operate in the afternoon)"
- "The New, Mighty Navigator"

The equipment names are similarly virile—Madison Avenue at its best: one is called "NEUROSTAR"; others, "MYSTRO," "CONCERTO," and "VIKING." One unit is billed as "a complete neurodiagnostic laboratory," promising neurometric analysis, brain mapping ("see events inside your patient's brain"), ambulatory EEG recording, evoked potentials, sleep laboratory tracings, and surgical monitoring. Practitioners are exhorted to "Equip Your Practice for Under 40K!" Some ads promise that the equipment will pay for itself in "just a month." Another rejoices that the computerized diagnostic machine even "fills out insurance reports ready for you to sign." Neurologists are urged to "leverage" their expertise by buying the equipment for their offices. Toll-free numbers for further information are included; perhaps one should be 1-800-GREED.

When I was in pediatric neurology fellowship training in the 1960s, one of my teachers called the phenomenon by which neurologists generate income by performing neurodiagnostic tests themselves *acute remunerative neurology*. He decried the practice, which fortunately was fairly rare then. Am I getting old, or do recent observations suggest a reappearance of the disorder?

Residents are being encouraged to take fellowships in EEG and EMG proficiency. The majority of journal ads for neurology positions insist "EEG/EMG capability strongly advisable." Translation: we need you to generate a portion of your income by doing these procedures. One recent advertisement for a neurologist in a large city read as follows: "Candidate must demonstrate competence in EEG, EMG, evoked potentials, and CAT scan interpretation." What ever happened to the history, neurologic examination, and neuroradiologists?

The entrepreneurial spirit also carries over to continuing education. The abstract of a course at a major national neurology meeting promises to teach neurologists how to make the area of study a "financially successful enterprise."

A business column in a recent medical news magazine suggests that a good marketing strategy for physicians is to send holiday presents to referring colleagues—fruit baskets, wine, or magazine subscrip-

tions are considered "standard physician etiquette." Another article notes, "You've got to think of ways to get your name up in lights." Visitors to the opening of an MRI facility are given souvenir copies of their own head scans to commemorate the momentous occasion. That could prove interesting in the social hour that often follows ("Wow, did you catch that atrophy?").

The prospects for other income-generating avenues in neurologic practice are limitless. A few come to mind immediately for marketing to patients and colleagues:

- A Polaroid copy of your MRI scan, suitable for framing (to show to your mother-in-law or boss to prove that there is something besides air and spinal fluid between your ears?)
- Neuroimaging kiosks in the malls and airports: "Get-a-scan-while-you-wait"
- A collage of color brain maps of the whole family (good for Christmas cards or the grandparents' scrapbook)
- A copy of your latest BEAM study to show your significant other (notice the maximal activity in the limbic system)

High-tech "hardware" advances in pediatric neurology have paralleled or even exceeded those in other aspects of medicine. I rejoice at the beautiful "windows to the brain" we now have available in the form of modern CT head scanning and MRI imaging. I will never miss subjecting infants and young children to the painful and potentially hazardous neurodiagnostic procedures of the 1960s.

But things have gotten out of hand. We all recognize the importance and necessity of paying the bills in office practice. The new array of neurodiagnostic tests is seductive. Who wouldn't like to "see" inside the young child's brain with a full-color "brain map"? However, too much emphasis is being placed on neurological marketing to generate income from such studies. In reality, the clinical indications for their use are relatively few.

Pediatricians should keep these developments in mind as they choose neurologic consultants. The costs of care for children with neurological disorders are heavily determined by the use of neurodiagnostic procedures. As long as some neurologists continue to generate significant portions of their income from the performance of these procedures, built-in conflicts of interest are inescapable. The modern child neurologist can be of most help to his or her pediatrician-colleagues by serving as a consultant—doing a history, performing a careful neurological examination, and recommending *pertinent* ancillary diagnostic tests, when clinically indicated.

Informed Consent for Lumbar Puncture

Jeffrey R. Botkin, MD, MPH

• Informed consent procedures are commonly employed prior to lumbar puncture. An understanding of the legal and ethical basis of informed consent is important in developing an acceptable approach to consent and in dealing with problems confronted when consent cannot be obtained. I review the current legal concepts in informed consent and their ethical foundation, and make recommendations to clinicians for obtaining consent for this common procedure in the ambulatory pediatric population.

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Despite the frequent use of consent procedures, many physicians remain uncertain about the legal and ethical requirements of informed consent. There is a growing literature on the theory and practice of informed consent,^{1,4} but there has been relatively little published in the medical literature that provides specific guidance to the clinician.

For editorial comment see p 885.

Unfortunately, the law and ethical theory are crude instruments for the guidance of physicians in their daily care of patients. As a result, there is inconsistency in our practice with respect to informed consent; we generally obtain consent for some procedures, such as lumbar puncture, while others, such as arterial puncture for blood gas measurement, are generally performed without consent. An understanding of the developing legal and ethical basis for informed consent will provide a rational foundation for consent practices and may foster a more consistent approach

based on a morally acceptable standard of care.

Lumbar puncture serves as an appropriate focus for this review since it is a common procedure performed in pediatric practice for which informed consent is usually obtained from the child's parent or guardian. Following a review of the legal and ethical aspects of informed consent, I will offer general recommendations for appropriate informed consent for lumbar puncture in the ambulatory pediatric population. Hypothetical cases will be presented to illustrate the issues, and the implication of these recommendations for other common procedures will be discussed.

THE ETHICAL BASIS OF INFORMED CONSENT

The philosophical and legal basis for informed consent was expressed in 1914 by Justice Cardozo: "Every human being of adult years and sound mind has a right to determine what shall be done with his own body."⁵ This right is rooted in the ethical principle of autonomy or self-determination. Ideally, informed consent is the process by which competent patients maintain informed control over their medical care.

The appropriate expression of patient autonomy in the contemporary patient-physician relationship remains a topic of debate; however, it is clear that there has been a significant transfer of control from the physician to the patient over the last century. The 1847 American Medical Association Code of Ethics stated: "The obedience of a patient to the prescriptions of his physician should be prompt and implicit. He should never permit his own crude opinions as to their fitness, to influence his attention to them."⁶ The expansion of choices in medicine over the century and the decline in unquestioned authority in our society have led to the conclusion that the patient's opinions, crude or other-

wise, are essential to defining the best course for individual welfare. The right of the patient to make informed choices on issues affecting health is now a fundamental component of the patient-physician relationship. To a large extent, this change in the clinical relationship with respect to informed consent has been driven by changes in legal standards.

LEGAL STANDARDS FOR INFORMED CONSENT

In general terms, the current legal standard requires the physician to disclose to the patient the diagnosis, the prognosis with and without treatment, and the alternatives for treatment with their attendant risks and benefits. While this standard will apply in the great majority of clinical circumstances, there are four recognized exceptions to the requirement for informed consent: (1) medical emergencies, (2) incompetent patients, (3) patient's expressed waiver of consent, and (4) therapeutic privilege.² A brief discussion of each of these exceptions is appropriate.

Informed consent is frequently deferred in medical emergencies. Urgent situations require decisive action and there is no time for a consent process. "Presumed consent" is invoked in emergencies with the assumption that most people would consent to reasonable attempts to save life or limb. Explicit refusals of care may also not be honored in emergency situations because the competency of the patient may not be ascertainable—the person who attempts suicide being an obvious example.

Waiver of consent applies to those situations when the patient *explicitly* transfers decision-making authority to the physician. Acceptance of a waiver is most appropriate *after* the full disclosure of relevant information. Physicians need not force patients to make decisions when patients are psychologically unprepared to do so. However, physi-

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cians should be reluctant to accept decision-making authority when the decisions are highly value laden.

The problem of the incompetent patient raises a number of complex issues. Strictly speaking, *competency* is a legal term, and in some circumstances the physician must turn to the courts for the determination of the patient's competency. In practice, physicians make implicit or explicit determinations of competency on a daily basis. If a patient is deemed incompetent, informed consent is generally obtained from the next of kin or the legal guardian. Thus, informed consent, albeit from surrogates, remains an integral part of the care of the patient. It is clear, however, that competency (in the nonlegal sense) is not an all-or-none phenomenon. Patients may be competent to understand basic choices with less than life-threatening consequences but unable to adequately comprehend complex choices with potentially grave consequences. Patients should retain control over that portion of their health care they fully understand.

Therapeutic privilege refers to the physician's prerogative of withholding information that he or she believes may be harmful to the patient. In a coronary care unit, for example, the medical staff may choose to withhold information from a competent patient about his or her condition and the therapeutic options while the patient is in a clinically unstable condition. Therapeutic privilege is a controversial exception, and the law remains unclear about the extent of this privilege.⁶ Therapeutic privilege should never be employed to override a competent patient's expressed wishes. Many commentators argue that therapeutic privilege should only be invoked if the anticipated harm to the patient is likely to be immediate and severe.

LEGAL THEORY

Two important transitions in the doctrine of informed consent have occurred over the past several decades. While consent per se has been a legal requirement for medical care at least since Justice Cardozo's influential opinion in 1914, the birth of *informed* consent dates to 1957. In the case of *Salgo v Leland Stanford Jr University Board of*

Trustees, the court established the physician's duty to disclose "any facts which are necessary to form the basis of and intelligent consent by the patient to the proposed treatment."⁷ Thus, for consent to be considered valid, the patient must be given sufficient information to understand the nature of the decision, although, as will be discussed, the definition of "sufficient information" remains unclear.

The second important transition involves the legal theory underlying informed consent. Many of the early informed consent cases were decided on the basis of the legal theory of battery. Battery is defined as the unconsenting "touching" of one individual by another. Under this legal theory, no harm needs to result from the touching—the physician would be liable if a procedure was performed for which consent had not been obtained, even if the patient experienced no harm from the procedure. In recent decades, the legal basis has shifted to a negligence theory, that is, malpractice. Under a negligence theory, a successful suit will be dependant on the plaintiff's ability to demonstrate five key elements in an informed consent case: (1) the physician must owe a duty to the patient to provide information, (2) breach of the duty must be demonstrated, (3) the patient must suffer harm, (4) the harm must represent the development of an undisclosed risk, and (5) had the patient been informed of the risk, he or she would not have consented to the procedure.⁸

Of particular importance to our discussion is the requirement that the patient be able to plausibly argue that he or she (or any reasonable person) would have refused the procedure if he or she had been informed of the risk. The corollary of this is the requirement for physicians to provide all the information that a reasonable person would require to make a decision. This has been termed the "reasonable person" standard of disclosure. (Some state jurisdictions require only that a physician provide the same information that other physicians provide to patients in similar circumstances. This is often a less stringent standard than the reasonable person standard.) Of course, it may be difficult for a physician or a jury to decide what level of risk a reasonable person would

require in a given clinical circumstance. It is clear, however, that the physician need not deliver a "polysyllabic discourse on all possible complications."⁹ There are no clear rules for physicians to follow in this respect; disclosure is guided by the facts of the individual case. It is fair to assume, however, that reasonable people would not forgo life-sustaining treatments due to remote risks of harm. Conversely, reasonable people might well forgo elective procedures due to risks of a small magnitude.

CONSENT FORMS

In the typical clinical context, the law does not require the signing of consent forms by patients.¹⁰ It is patient understanding and active participation in decision making that is significant to the law and ethics of informed consent. Consent forms have two principal values: (1) They can foster patient education with respect to the proposed treatment or procedure. To promote this goal, consent forms must be clearly and simply written using lay terms and should be customized for the proposed procedure or treatment.^{11,12} Education for more complicated treatments or procedures may be best handled in written form. (2) Signed consent forms may provide some legal protection for physicians if the forms are used as documentation that an informed consent process has occurred. A signed form itself, however, provides no protection if the patient can plausibly claim that the diagnosis and the risks of, benefits of, and alternatives to the procedure were not adequately discussed prior to the signature and/or the signature was obtained without an opportunity to read and understand the form.¹³ Patient understanding and participation can be documented by a signature, but the clinical reality is that signatures can be obtained easily from many patients with little or no discussion of the relevant information.¹⁴ A court of law may view the signature accordingly. Clear documentation in the physician's records noting a discussion of consent is adequate in lieu of a consent form from a legal and ethical perspective. (Hospital or department regulations may require consent forms, as do institutional review boards in research settings.) True informed

consent is the physician's best legal defense with or without a signed consent form.

INFORMED CONSENT FOR CHILDREN

The informed consent process in the pediatric population has important differences from the process with competent adults. Young children are not competent to consent to treatment or procedures. (The competency of older adolescents is a complex issue from both the legal and ethical perspectives and will not be addressed in this discussion.¹⁵) It is the responsibility of parents or guardians to provide informed consent for children. The discretion of parents is limited, however. Competent adult patients clearly have the legal and moral right to refuse any or all treatments for any reason they deem sufficient—even life-sustaining procedures. Parents, however, do not have the same absolute right to refuse treatment or procedures on behalf of their children.¹⁶ For example, parents have not been permitted by the courts to refuse chemotherapy for a child with leukemia,¹⁷ to refuse removal of an optic glioma,¹⁸ or to refuse blood transfusion when the child's life is in imminent danger.¹⁹ Conversely, courts have refused to rule against the wishes of parents when the child's medical condition is not serious or life threatening.²⁰⁻²² The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research²³ and the Committee on Bioethics of the American Academy of Pediatrics²⁴ have supported limitations on parental authority when the health of a child is in jeopardy. These precedents suggest that parental discretion is broad but that it does not include choices that may seriously threaten the welfare of the child.

LUMBAR PUNCTURE

With this background we can look more specifically at the issue of informed consent for lumbar puncture in the ambulatory pediatric population. These comments will pertain to lumbar puncture as a diagnostic procedure for suspected intracranial infection and do not pertain to lumbar puncture as a therapeutic measure. Also, the risks and benefits of lumbar puncture in sick

neonates is more complex than in the ambulatory population and will not be dealt with here.

Lumbar puncture is principally used for the diagnosis of meningitis, and it must first be noted that there are no appropriate alternatives to the lumbar puncture for establishing this diagnosis. The advantages of making a rapid diagnosis are obvious: treatment can be initiated, pathogens can be identified and sensitivities established, complications and sequelae of the illness can be anticipated, and appropriate public health measures can be instituted when indicated. Bacterial meningitis remains a life-threatening illness despite antimicrobial therapy, with a mortality in neonates of between 15% and 20%.²⁵ Mortality beyond the neonatal period is less than 10%; however, neurologic sequelae may be present in as many as 50% of the survivors, including hearing deficits, seizures, motor impairments, and learning and developmental disabilities.²⁶ Delay in the diagnosis of meningitis is a recognized risk factor for disease sequelae.²⁶ The benefits of lumbar puncture are clear: it is an essential procedure for the diagnosis of a serious and potentially life-threatening illness.

Unfortunately, data do not exist to accurately assess the risks of lumbar puncture in the pediatric population. The adverse reactions listed by Klein et al²⁵ include pain from the procedure itself, headache, bleeding into the tissues surrounding the spinal column or into the cerebrospinal fluid, and herniation of the temporal lobes through the tentorium or herniation of the cerebellar tonsils through the foramen magnum. Other reported risks include local infection, transient or persistent paresthesias or leg numbness, cranial nerve palsies, and seeding of the meninges in bacteremic patients.²⁷ The subjective nature of some of these complications will make them impossible to quantify in the young population. Marton and Gean²⁷ have provided a recent review of the literature on lumbar puncture with data principally from the adult population. The reported incidence of headache is quite variable, depending on the technique and position used, but is generally believed to be in the 10% to 25% range. In those receiving spinal anesthesia, 13% had immediate painful par-

asthesias, 0.2% had persistent paresthesias, and 0.7% had leg numbness that disappeared within 1 year. Transient cranial nerve palsies were reported in 0.02% of patients.

"Traumatic taps" are frustratingly frequent; Morton and Gean²⁷ report an incidence of 20%. The vast majority of these are of no clinical significance other than the difficulty created in interpreting the cerebrospinal fluid results. However, spinal subdural or epidural hematomas can develop in those patients with coagulation disorders and these can produce serious sequelae. Ruff and Dougherty²⁸ reported an incidence of major complications of 6.7% in 342 patients given anticoagulants after lumbar puncture, including 1.5% who developed paraparesis. A traumatic tap increased the risk of a major complication in this group. The risk of a symptomatic hematoma in the pediatric population without known coagulation disorders is unknown, but based on the above data the incidence of serious sequelae must be exceedingly small.

A potential risk of inducing meningitis by lumbar puncture in the bacteremic child was identified by Teele et al.²⁹ However, that study did not control for other clinical variables, and it is possible that the association between lumbar puncture and subsequent meningitis was an artifact produced by the selection of the sickest patients for lumbar puncture. Shapiro et al³⁰ evaluated this issue in 310 children with occult bacteremia in a study that controlled for a number of variables. Their results led them to conclude that the risk of meningitis from lumbar puncture in bacteremic patients was insignificant and was outweighed by the information obtained from the procedure.

The most serious complication of lumbar puncture is herniation. This complication may be fatal even with prompt recognition and treatment. Dodge and Swartz³¹ diagnosed herniation in 10 of 29 patients dying of acute bacterial meningitis. The overall incidence of herniation in their adult and pediatric cases of bacterial meningitis was 5.1%. One case of herniation occurred prior to lumbar puncture, 3 occurred within 2 hours of the procedure, and 5 occurred more than 2 hours later.

In the largest reported pediatric se-

ries to date, Horowitz et al³² found an incidence of herniation of 6% in 302 infants and children admitted to a tertiary care center for acute bacterial meningitis. In this series, 1 patient developed herniation immediately following lumbar puncture and another 7 of 18 patients with herniation developed their symptoms within half an hour of admission. This study was performed by reviewing charts retrospectively for cases over a 9-year period, so the quality of the data may be limited.

The review of the literature on lumbar puncture by Marton and Gean²⁷ suggests that the incidence of herniation in adult patients with evidence of raised intracranial pressure is in the general range of 1%.

Due to the risk of herniation, however, it is generally recommended that lumbar puncture be withheld pending further evaluation in those patients who exhibit indications of raised intracranial pressure. These indications include altered level of consciousness, a history of significant head trauma, Cushing's triad, papilledema, focal neurologic signs, neurologic signs preceding the acute illness such as progressive headache or persistent vomiting, or an abnormal computed tomographic scan.^{25,33,34} In their pediatric series, Horowitz et al³² were unable to identify clinical criteria on a patient's admission to the hospital that would have predicted herniation.

The difficulty with these data is that they do not permit an assessment of the cause-and-effect relationship between lumbar puncture and herniation. Herniation is a well-recognized complication of the primary disease process in meningitis. Without a controlled prospective study, it is impossible to determine what proportion of patients with herniation would have developed it without the procedure. In addition, our estimation of risk for consent purposes must be based on all children undergoing lumbar puncture, which is a much larger number than those subsequently diagnosed with bacterial meningitis.

Based on this limited information, we can conclude that the risk of herniation attributable to lumbar puncture is unknown, but is probably quite small in the ambulatory pediatric population for which the procedure is indicated.

In summary, the lumbar puncture is a

safe procedure for which there are no acceptable alternatives for the diagnosis of life-threatening intracranial infections. These features of the illness and the procedure will guide the informed consent process and will place some limitations on a parent's ability to refuse the procedure.

RECOMMENDATIONS FOR INFORMED CONSENT

These recommendations are intended to provide general guidance to physicians based on the legal and ethical considerations cited above. To my knowledge, there have been no legal cases that address the physician's specific obligations in this particular clinical circumstance. These recommendations are therefore based on analogy and precedent, which are fundamental to legal decision making but provide no guarantees for future rulings. Each legal case is always considered in light of the particular facts involved.

When a lumbar puncture is clinically indicated for suspected meningitis, the parents should be fully informed by the physician about the child's clinical condition and the concern about meningitis. Meningitis should be explained in lay terms, and parents should be aware that it is a serious condition. Specific details of morbidity and mortality from meningitis need not be presented prior to the definitive diagnosis, although parents' questions should be answered in full. The need for a lumbar puncture, the nature of the procedure, and the lack of available alternatives should be discussed. Parents are often alarmed by the description of the lumbar puncture, but the physician can reassure parents about the safety of the procedure. Common complications, such as local pain and headache, should be discussed. Parents should be informed that serious complications of the procedure are rare and that the greatest risk to the child lies with an undiagnosed meningitis. The specific nature of the remote risks need not be discussed unless the parents ask. In legal terminology, these remote risks should not be "material" to a reasonable person's decision to consent to the procedure in these clinical circumstances.

Signing of a consent form by the parents is not necessary if the above discus-

sion has taken place and is briefly documented in the progress chart. If the use of a form is preferred, it should be designed to relate information specific to lumbar puncture in language comprehensible to the individual signing the form. Parents must be given the opportunity to read the form and ask questions about its content. It should be emphasized again that the consent form will not provide the physician with legal protection if the parents can plausibly claim that they did not know what they were signing.

Two hypothetical patient histories follow that represent problems in obtaining consent and illustrate some of the legal and ethical dimensions discussed.

1. Alisa is a 20-month-old previously healthy female infant who presents to a pediatrician with a 4-day history of rhinorrhea and a 2-day history of fever and irritability. The child is febrile and appears lethargic but responsive. Her physical examination is notable for nuchal rigidity. There is no other focus of infection apparent on physical examination; no focal neurologic signs are apparent and there is no papilledema. Alisa is accompanied by a foster parent who has temporary custody of the child. The foster parent has not been given a release for medical treatment and the social worker assigned to the case is unavailable. Should the physician obtain court authorization before proceeding with the lumbar puncture?

2. The same child presents to the physician's office in the same physical condition, but she is now accompanied by her parents who have legal custody. After a full discussion of the child's condition, the parents refuse consent for lumbar puncture.

In the first scenario, a problem arose with consent because there was no appropriate decision-making authority available for the child. In this circumstance, if the parents can be contacted without delay, this is certainly the appropriate next step. If the parents are unavailable, the time necessary to obtain an authorization from court would jeopardize the welfare of the child. The physician should proceed with lumbar puncture and appropriate care for the child, and court approval can be pursued later if necessary. The physician will not

be liable for malpractice for lack of consent if he or she has used good clinical judgment, even if harm subsequently develops from the care rendered.

The second scenario is a problem of parental refusal of lumbar puncture despite clear medical indications. In this circumstance, additional discussion with the parents is warranted. An exploration of the parent's beliefs may uncover misconceptions about the potential serious nature of the child's condition, the motivation of the physician, or the risks of the procedure. A second opinion by a colleague may help allay the parent's unjustified fears. If the parents continue to refuse the procedure, the physician's primary obligation is to the welfare of the child. Unless a court order can be obtained promptly, lumbar puncture and treatment should proceed without consent, and court approval can be sought for continued care if necessary.

When meningitis is suspected, the parents' discretion to accept or reject diagnosis and treatment is limited. A successful negligence suit based on lack of informed consent would require that the child suffer a net harm from the procedure and parents would have to claim that reasonable people would not have consented to the procedure under the given circumstances. If the physician has exercised good clinical judgment, this should not be a plausible claim. In general, a physician taking urgent action with skill and good conscience for the significant welfare of a child is unlikely to be the victim of a successful malpractice suit for lack of consent. Failure to provide appropriate care for a child due to misguided fears of legal liability is the greater moral and legal transgression.

These principles should also hold true for those clinical circumstances when meningitis is less likely than in the scenarios presented. The child who is febrile without an apparent cause on examination is the most common candidate for lumbar puncture, and, of course, the great majority of taps are negative. Nevertheless, if the physician has used reasonable clinical judgment in the determination that a lumbar puncture is indicated, there should be no legal repercussions if the procedure is performed without consent, even if harm develops from the procedure (if competently performed).

IMPLICATIONS FOR OTHER PROCEDURES

With respect to informed consent, it is my opinion that lumbar puncture constitutes a "paradigm case," in which the resolution of the legal and ethical issues is clear and, as such, the case can serve as a model for decision making in other clinical circumstances. If another procedure is similar to lumbar puncture in all relevant ways, then the standards of consent for the procedure will also be similar. Conversely, if a procedure differs in relevant ways from lumbar puncture, the differences can be analyzed with respect to the legal and ethical principles of informed consent, and a different standard of consent can be utilized accordingly. Understanding the technical, legal, and ethical foundations of a paradigm case thereby assists in guiding consent for a variety of clinical circumstances.

The features of the lumbar puncture that make it a paradigm case are the lack of reasonable alternatives, the emergent nature of the procedure, and the

high benefit-to-risk ratio, including the potential benefit of the preservation of life. In general, all of these features would need to be present for a physician to override the parents' refusal of the procedure or treatment without legal authorization. Other procedures performed by pediatricians that would probably meet these criteria, depending on the clinical circumstance, would include a paracentesis for suspected peritonitis and a thoracentesis for pneumonia with effusion and respiratory failure. A myringotomy in a patient with mastoiditis or a bladder tap in a febrile infant would not meet the above criteria due to the alternatives and/or the less serious nature of the conditions. The risks disclosed should always be guided by what a reasonable person would require to reach a decision in the situation at hand, which will depend on the potential benefits of the procedure as well as the nature and the magnitude of the specific risks involved. No specific guidelines can replace the physician's good judgment in this respect.

The lack of complete parental authority in emergent situations should not be taken as a liberty to give perfunctory attention to informed consent. The advantages of informed consent extend beyond its legal bounds. Informed parents who are active participants in care decisions will have greater trust in the physician and a better appreciation of the strengths and limitations of modern medicine. A relationship of mutual respect between parents and physicians will ultimately benefit parents, physicians, and children.

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Book Review

Peace of Mind During Pregnancy, by Christine Kelley-Buchanan, 384 pp, \$24.95, New York, NY, Facts on File Publications, 1988.

Between 40% and 90% of all women in the Western world use at least one medication during pregnancy. Since the thalidomide tragedy, every drug has been viewed as a potential teratogen. In fact, only roughly 20 xenobiotics are proved human teratogens. In a recent study conducted in Toronto, Canada, we showed that women consulting the Motherisk program (an antenatal consultation service for drug, chemical, and radiation exposures) assign themselves a 25% teratogenic risk when exposed to nonteratogenic drugs.

Clearly, there is a need for authoritative information on the risk of exposure to drugs, chemicals, radiation, or infection in pregnancy. Although it is facile to say, "Do not use during pregnancy," more than 50% of the women contacting the Motherisk program do so after realizing that conception occurred while being exposed to the agent in question. For these women, the notion "do not use during pregnancy" may easily translate to "terminate pregnancy if you have been exposed." It is equally important that the expectant mother and her family not only understand available information, but comprehend the limitations in the type of epidemiologic research that leads to current recommendations.

Ms Kelley-Buchanan's book deals very well with these issues. The title is somewhat misleading, seeming to address laypeople but risking dismissal by the medical professional as "too simplistic." Not so. This is a very professional book, more so than most available A through

Z teratology handbooks that do not weigh data, but simply quote them. The book is written by a genetic counselor who obviously has weighed the safety/risk ratios of environmental agents and has integrated and explained this information on a daily basis. Most teratology texts lack this practical clinical approach.

The text not only is excellent in its approach but is scientifically sound. Relevant, current data are presented, and methodological weaknesses are exposed. For example, most scientific literature on lithium teratogenicity is based on the Danish lithium registry. Pertinent methodologic flaws in the registry data collection and the background incidence of these malformations in the general population are discussed. No other current teratology handbook includes this important information.

Because of the thorough, analytic discussion, the book reviews only 200 agents. It does not profess to be a comprehensive compendium of all environmental exposures in pregnancy. Instead, all known and suspect human teratogens are included as well as the common drugs likely to be used by women of childbearing age. This book has the rare potential of becoming an important reference for both laypeople and health professionals alike.

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Perinatal Outcome of Infants Exposed to Cocaine and/or Heroin In Utero

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• While cocaine is now used much more frequently than heroin by women of childbearing age, we have found that a significant number of mothers have abused both drugs during their pregnancy. We studied 86 infants who were born to women with a history of cocaine and/or heroin use during pregnancy. The newborns were observed over a 5-day hospital period using a standardized abstinence scoring system and urine drug screening of both mother and infant. Of these, 35 had maternal and/or newborn urine test results that were positive for cocaine only (cocaine group), 14 that were positive for heroin only (heroin group), 17 that were positive for both cocaine and heroin (cocaine/heroin group), and 20 that were negative for both, although the mothers admitted to cocaine use during their pregnancy (cocaine history group). In approximately half of the mother/infant pairs, the

results of the urine drug tests were discordant. Microcephaly and growth retardation occurred most frequently in the infants in the cocaine group (17% and 27%, respectively). Microcephaly was also found to be significant in the infants in the cocaine/heroin group. Signs of drug withdrawal occurred in all four drug-exposed groups. Mild withdrawal occurred in 26% of infants in the cocaine group, 21% of the infants in the heroin group, 47% of the infants in the cocaine/heroin group, and in 30% of the infants in the cocaine history group. Withdrawal requiring treatment occurred in 6% of the infants in the cocaine group, 14% of the infants in the heroin group, 35% of infants in the cocaine/heroin group, and 5% of the infants in the cocaine history group. The use of heroin with cocaine has a synergistic effect on the behavior of the newborn.

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Both cocaine and heroin are used with alarming frequency by women of childbearing age. Although the majority of the infants that we now see with prenatal exposure to illicit drugs are born to mothers who are cocaine abusers, almost one fourth of them are born to mothers who are abusers of both cocaine and opiates. While there is a substantial amount of information available about the effects of prenatal exposure to heroin, less is known about the effects of prenatal exposure to cocaine. Virtually nothing is published about the effects of prenatal exposure to combined cocaine and opiates. It was to characterize infants born to mothers who used both cocaine and opiates during their preg-

nancy that we undertook this study.

The effects of cocaine on growth and behavior have recently been described.¹⁻³ Madden et al⁴ described eight newborns with positive urine test results for cocaine who did not show signs of withdrawal; their study was performed without a standardized abstinence scoring system. Bingol et al⁵ found significantly decreased birth weight and head circumference in a group of 160 infants whose mothers used cocaine during their pregnancy. Chasnoff et al⁶ found no difference between the birth weight and head circumference of 23 infants born to mothers who used cocaine during pregnancy and those born to a control group. They did find an increased incidence of tremors and interactive behavioral abnormalities in the infants born to mothers who used cocaine, although they did not report withdrawal requiring treatment. Naeye et al⁷ found that infants exposed to heroin frequently are growth retarded, show meconium staining, and

are premature. The frequency and severity of heroin withdrawal has been compared with that of methadone hydrochloride and has been found to be just as frequent but less severe.⁷ Ryan et al⁸ found that infants exposed to both cocaine and methadone had the same frequency of abstinence scores as a group of infants exposed to methadone only. Oro and Dixon⁹ reported that infants exposed to cocaine and narcotics have the highest morbidity compared with infants exposed to cocaine or narcotics alone.

We undertook this prospective study of newborns who had been prenatally exposed to cocaine and/or heroin to determine if urine drug screening should be extended to both mother and infant to improve detection, to examine the relative impact of these drugs on fetal growth, abnormal behavior, or withdrawal, as well as to determine whether infants exposed to both drugs showed any signs of synergistic effects.

PATIENTS AND METHODS Study Population

We collected data on all infants who were delivered at Highland General Hospital, Oakland, Calif, during a 28-week period. During the study period there were 1129 infants born alive. We initially identified 108 newborns as study candidates by either a history of maternal drug abuse or a suspicion of maternal drug abuse. The remaining 1021 infants, including 985 who were born at term and 36 who were born prematurely, were thought to be drug free. Seventeen newborns who were initially identified because of suspected maternal drug abuse were subsequently excluded because their mothers denied the use of cocaine and heroin, and both maternal and newborn urine tests were negative for cocaine and heroin. An additional 5 newborns were excluded when maternal urine screens were inadvertently not obtained. The remaining 86 newborn/mother pairs with documented exposure to

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Table 1. — Results of Urine Drug Tests on 86 Mother/Newborn Pairs in the Study Population*

Drugs Detected in Urine	Drug Group			Cocaine History (n = 20)
	Cocaine (n = 35)	Heroin (n = 14)	Cocaine/Heroin (n = 17)	
Cocaine	35	0	17	0
Heroin	0	14	17	0
Methadone	0	1	0	0
Methamphetamine	2	3	3	1
Tetrahydrocannabinol	7	1	3	2
Alcohol	0	1	0	0

*Values represent the number of pairs where the urine of the mother and/or her newborn contained the specified drug.

cocaine and/or heroin are included in this report.

All women who delivered infants during the 28-week period were questioned about drug abuse during the pregnancy by an attending obstetrician at the time of admission, by an attending pediatrician (R.F.) at the time of the infant's birth, and by a social worker before discharge. Study newborns were defined as those who met one of the following criteria: (1) infants born to mothers who admitted the use of any illicit drugs during pregnancy; (2) infants born to mothers who gave a negative history of illicit drug use, but with such signs of drug abuse as needle track marks or withdrawal symptoms; or (3) infants who showed signs that were compatible with neonatal withdrawal.

Study newborns were compared with infants with no history of drug exposure during pregnancy. Our study was approved by our hospital institutional review board for studies involving human subjects.

Study Protocol

We estimated the gestational age of the newborns by the modification by Ballard et al¹⁰ of the Dubowitz method. We calculated the mean and SD for birth weight and head circumference of the infants born at term without a history of drug exposure who were delivered during the study period. We defined growth retardation as a birth weight that was more than 2 SDs below the mean of these infants. Similarly, we defined microcephaly as a head circumference more than 2 SDs below the mean.

All study newborns were admitted to the nursery where they were observed and treated according to our standard protocol for infants at risk for withdrawal. They were observed for a minimum of 5 days, during which time they were scored for signs of drug withdrawal. Urine samples were obtained from the mother at the time of her admission to the hospital and from the newborn at first void in the nursery for drug screening. Maternal urine samples required 50 mL, and the

infant urine sample required 10 mL, which was collected in all cases. None of the women received morphine or other opiate medication while in the hospital and before the delivery of their newborn or before the time the urine samples were obtained.

The urine samples from the infants and their mothers were tested for the presence of cocaine, heroin, methadone, methamphetamine, tetrahydrocannabinol, and alcohol. The drugs were identified by thin-layer chromatography, including a step to convert bound morphine to free morphine. Heroin was identified as urinary morphine. Results were confirmed by enzyme immunoassay. Sensitivity is 1 mg/L of urine for the thin layer chromatography procedure and 0.3 mg/L (95% confidence interval) for the enzyme immunoassay for both cocaine and heroin. The results of the urine tests were not known by the nurses who performed the abstinence scoring.

Abstinence Scoring

We assessed drug withdrawal by the abstinence scoring system reported by Finnegan,¹¹ which measures 21 signs of drug withdrawal, including increased tone, tremulousness, tachypnea, decreased sleep time, and feeding disturbances. The study newborns underwent scoring every 4 hours, except when scores exceeded 12, which suggested moderate or severe withdrawal. In these cases, they underwent scoring every 2 hours.

All newborns with a score greater than 12 recorded three times in succession (with scoring done every 2 hours) were examined by a second scorer to ensure that they had unequivocal signs of moderate to severe withdrawal. They were then treated for withdrawal.

Abstinence scores were also assigned to a group of 29 control infants who were born by cesarean section during the study period to mothers without a history of drug use. These newborns were used to demonstrate the validity of the scoring system. Newborns who

were delivered by cesarean section were chosen as a control group because they were expected to remain in the nursery for 5 days. All scorers underwent a course of instruction before the beginning of the study to standardize the evaluation of abstinence symptoms.

Treatment

The decision to treat all newborns who had a score above 12 was reached after a 4-month trial period before our study in which the clinical assessment of withdrawal by the attending pediatrician (R.F.) was compared with abstinence scores. Newborns suffering from withdrawal were treated with phenobarbital sodium,¹² so that blood levels could be monitored. All newborns had a complete blood cell count, and serum calcium, magnesium, and glucose levels were obtained before treatment to rule out other causes of signs of withdrawal.

Statistical Analysis

We compared groups with a Fisher Exact Test. $P < .05$ was considered significant. All data are represented as mean (\pm SD).

RESULTS

The 86 newborn/mother pairs were placed in one of four groups. Table 1 lists the results of the urine drug tests of the infants in these four groups. The first group (cocaine group) consisted of 35 newborns in whom the urine screen results of either the mother and/or the newborn were positive for cocaine but negative for heroin. The second group (heroin group) consisted of 14 newborns in whom the maternal and/or newborn urine screen results were positive for heroin but negative for cocaine. The third group (cocaine/heroin group) consisted of 17 newborns with maternal and/or newborn urine screen results positive for both cocaine and heroin. The fourth group (cocaine history group) consisted of 20 newborns whose mothers admitted to cocaine use at some time during their pregnancy, but for whom both the maternal and newborn urine screen results were negative for cocaine and heroin. These four groups were compared with the 1021 infants born to mothers without a history of drug use during pregnancy (no drugs group).

The results of many of the maternal and newborn urine screens were discordant for both cocaine and heroin (Table 2). In only 50% of the cases where maternal and/or infant test results for co-

Table 2.—Urine Drug Test Results Showing the Frequency of Discordant Results for the Mother and Her Infant*

Group	Drug Group			
	Cocaine (n = 35)	Heroin (n = 14)	Cocaine/Heroin (n = 17)	Cocaine History (n = 20)
Cocaine in urine				
Mother only	8	0	3	0
Infant only	9	0	6	0
Mother and infant	18	0	8	0
Heroin in urine				
Mother only	0	7	6	0
Infant only	0	3	2	0
Mother and infant	0	4	9	0

*Values represent the number in which drug was found in urine.

Table 3.—Frequency of the Most Common Signs of Abstinence in Each Group*

Sign	Drug Group				
	Cocaine (n = 35)	Heroin (n = 14)	Cocaine/Heroin (n = 17)	Cocaine History (n = 20)	Control (n = 29)
Hypertonia	91	79	87	85	28
Hyperactive Moro reflex	32	43	50	15	0
Tachypnea	21	14	53	0	3
Loose stools	18	22	6	6	0
Decreased sleep	15	7	13	5	0
Excessive suck	12	22	25	10	0
Nasal stuffiness	6	0	31	20	0
Poor feeding	0	7	0	20	0

*Values are expressed as percents.

caine were positive were both the maternal and infant urine test results positive. Similarly, only 42% of the maternal/infant pairs who had positive test results for heroin had positive test results for both the maternal and infant urine.

Abstinence Scores

Table 3 shows the eight most common signs and symptoms recorded in each of the drug groups. Tremors and hypertonicity were found most frequently; the other signs and symptoms are recorded in decreasing order of frequency.

Figure 1 shows the distribution of abstinence scores in each group of newborns. A score of less than 9 was interpreted as normal and a score between 9 and 12 was interpreted as mild withdrawal. A score greater than 12 was interpreted as moderate to severe withdrawal. Infants with a score greater than 12 were treated for drug withdrawal. Twenty-four (69%) of the 35 newborns in the cocaine group, 9 (64%) of the 14 newborns in the heroin group,

3 (18%) of the 17 newborns in the cocaine/heroin group, and 13 (65%) of the 20 newborns in the cocaine history group had scores less than 9. All 29 newborns in the cesarean section group had scores less than 9. Scores between 9 and 12 occurred in 9 of the newborns in the cocaine group (26%; $P < .005$, compared with the cesarean section control group), 3 infants in the heroin group (21%; $P < .05$, compared with the cesarean group), 8 infants in the cocaine/heroin group (47%; $P < .0001$, compared with the cesarean group), and in 6 infants in the cocaine history group (30%; $P < .005$, compared with the cesarean group).

Table 4 shows the number of infants treated with phenobarbital for each of the drug groups. One infant in the cocaine group had a seizure and was treated with phenobarbital before reaching an abstinence score of 13. No infant in any of the other groups had a seizure. Six infants in the cocaine/heroin group (35%; $P < .01$, compared with the cesarean group) had scores above 12

and were treated for withdrawal for an average of 21 days (range, 13 to 33 days).

Growth Retardation

Figure 2 shows the percentage of infants born at term in each group who were growth retarded based on the mean (\pm SD) weight of the 985 infants born at term in the no drugs group. Five (17%) of the 30 newborns born at term in the cocaine group (birth weight, 2820 ± 356 g), 1 infant (8%) of the 12 in the heroin group (3167 ± 646 g), 1 infant (7%) of the 15 in the cocaine/heroin group (2999 ± 354 g), and 1 infant (5%) of the 20 in the cocaine history group (3118 ± 474 g) had growth retardation. Twelve (1%) of the 985 newborns born at term without a history of drug exposure (3351 ± 469 g) had growth retardation. The difference between the incidence of growth retardation in the cocaine group and the no drugs control group was highly significant ($P < .0001$). The difference in the incidence of growth retardation among the other three groups and the no drugs control group was not significant.

Microcephaly

Figure 2 shows the percentage of newborns born at term in each group who were microcephalic based on the mean (\pm SD) head circumference of the 985 infants born at term in the no drugs group. Eight (27%) of the 30 newborns born at term in the cocaine group (head circumference, 32.3 ± 1.5 cm), 2 (17%) of the 12 infants in the heroin group (33.2 ± 1.8 cm), 3 (20%) of the 15 infants in the cocaine/heroin group (32.6 ± 1.3 cm), and none of the 20 infants in the cocaine history group (33.8 ± 1.2 cm) were microcephalic. Thirty-six (4%) of the 985 newborns born at term in the no drugs group (34.0 ± 1.5 cm) were microcephalic. The incidence of microcephaly was significantly higher in the cocaine group ($P < 10^{-4}$) and in the cocaine/heroin group ($P < .02$) than in the no drugs group.

Clinical Outcome

There were no significant differences between the 86 newborns in the study and the 1021 no drugs controls for any of the following characteristics: age, sex, race, 5-minute Apgar scores of less than

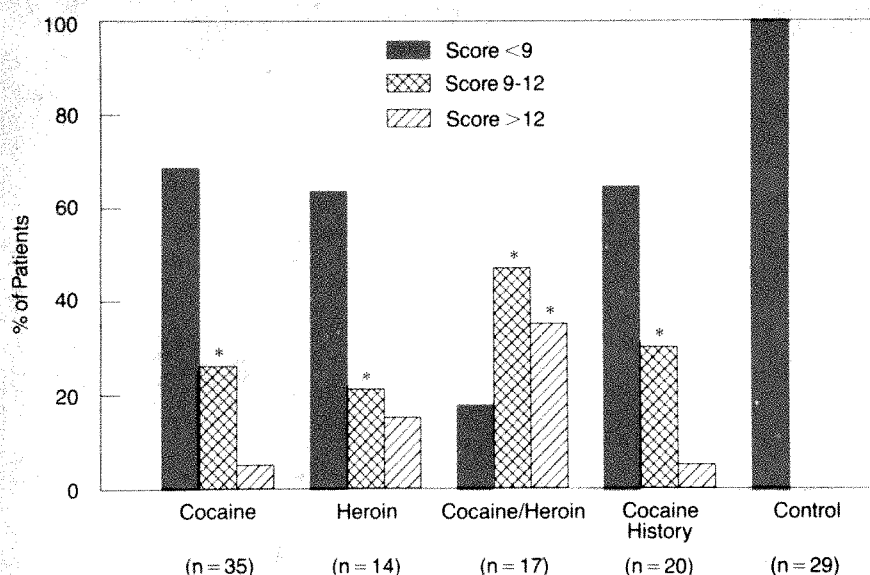


Fig 1.—Abstinence scores for infant groups as assessed by the Finnegan method.¹¹ Scores of less than 9 are defined as no withdrawal, 9 to 12 as mild withdrawal, and more than 12 as moderate or severe withdrawal. Asterisk indicates $P < .05$, when compared with the cesarean section control group by a Fisher Exact Test.

Table 4.—Percent of Infants Who Were Treated for Signs of Withdrawal, and the Mean Duration of Treatment

	Drug Group			
	Cocaine (n=35)	Heroin (n=14)	Cocaine/Heroin (n=17)	Cocaine History (n=20)
Treated, %	6	14	35	5
Duration of treatment, d	2	14	21	18

7, sepsis, congenital malformations, and need for transfer to a tertiary care nursery.

Maternal smoking occurred in 9 (82%) of 11 of infants in the cocaine group who were small for gestational age. All infants who were small for gestational age in the other three groups had mothers who smoked cigarettes. Five (14%) of the 35 infants in the cocaine group were born prematurely, compared with 36 (4%) of the 1021 of those in the no drugs control group ($P < .01$). Prolonged rupture of membranes (>24 hours) was found in 4 of 5 premature cocaine-exposed newborns, 1 of whom had evidence of chorioamnionitis on placental examination. None of the 4 premature heroin-exposed infants had prolonged rupture of membranes, but 1 did have chorioamnionitis.

Meconium staining of the amniotic fluid occurred in 99 (10%) of the 1021 infants in the no drugs control group compared with meconium staining in 12 (34%) of the 35 newborns in the cocaine

group ($P < .0002$), 5 (36%) of the 14 newborns in the heroin group ($P < .01$), 7 (41%) of the 17 newborns in the cocaine/heroin group ($P < .001$), and 6 (30%) of the 20 newborns in the cocaine history group ($P < .05$).

COMMENT

We have shown that prenatal cocaine and/or heroin use is associated with significant abnormalities in the infant, including elevated abstinence scores, growth retardation, microcephaly, prematurity, and meconium staining of the amniotic fluid. The results show that cocaine and heroin appear to be synergistic in causing abnormal behavior of withdrawal; less than 20% of the infants exposed to both cocaine and heroin had Finnegan¹¹ scores of less than 9. This was a significantly greater incidence of abnormal Finnegan scores than had occurred in infants exposed to either cocaine alone or heroin alone. Although we found that infants in both the cocaine group and the cocaine/heroin group had

significant growth retardation compared with a drug-free group, we saw no synergistic effect of cocaine and heroin on the incidence of growth retardation or microcephaly to confirm results of a recent study that showed that abusers of cocaine alone are no more likely than abusers of multiple substances to have growth-retarded infants.¹⁹

There are problems with defining a group of infants exposed in utero to drugs solely on the basis of maternal history. Mothers are well known to be poor historians about their drug use during pregnancy.¹⁴ We feel that in our study the problem of inaccurate histories was decreased by having the maternal drug history obtained by three separate individuals who were experienced in obtaining drug histories. If there were women who had used cocaine during their pregnancies who were incorrectly classified as having used no drugs, this would artificially lower the significance of our findings, rather than contribute to them.

The marked disparity between the results of maternal and neonatal urine drug tests is of special concern. The reason for this disparity is not entirely understood, but may represent individual differences in the metabolism and clearance of the drugs, collection techniques, or sensitivity of the urine screen.^{15,16} We have found that mothers who abuse either cocaine or heroin often abuse other street drugs. The use of thin-layer chromatography as a urine screen in both mother and infant was necessary to screen for all drugs used by the mother before delivery, but many false-negative results may occur secondary to the low sensitivity of the test.¹⁶ We found that in 35% of infants in the cocaine history group, abstinence scores were elevated but urine screen results were negative. Cherukuri et al¹⁷ found that in newborns of mothers who use "crack," 25% were symptomatic but had negative urine screening results, whereas another 35% of newborns had positive screening results and no symptoms of withdrawal using the more sensitive multiple enzyme immunoassay technique urine drug test. The mother's urine was not screened. These findings demonstrate the necessity of obtaining both maternal and neonatal urine drug tests when evaluating an infant for pos-

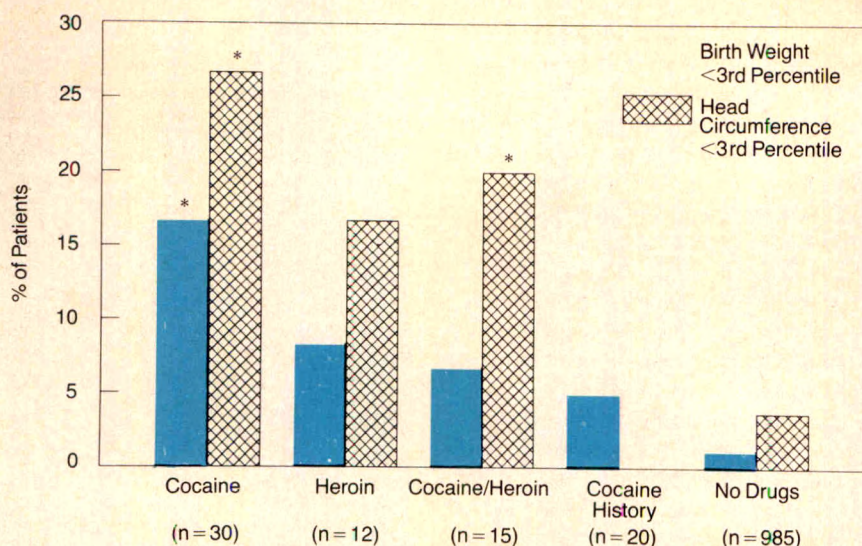


Fig 2.—Percent of infants born at term with birth weight or head circumference more than 2 SDs below the mean for infants without drug exposure who were delivered during the study period. Asterisk indicates $P < .05$, when compared with the no drugs group by a Fisher Exact Test.

sible drug exposure, but also warn that the results of the urine screen, particularly when negative, must be interpreted in light of the infant's clinical status.

We used the abstinence scoring system devised by Finnegan¹¹ to quantitate the presence and degree of withdrawal. All scorers were trained and were known to be able to score infants accurately. Although they were not blinded to which infants were in the cesarean group and which were in the study group, they were ignorant of the results of the urine tests. That all of the infants in the cesarean group had scores less than 9 suggests that this scoring system reliably separates infants with signs of withdrawal from those without.

It is not clear whether elevated abstinence scores really indicated withdrawal or whether they indicated some other neurologic abnormality. There is considerable evidence that repeated exposure to cocaine can cause long-lasting abnormalities by a mechanism, or mechanisms, other than withdrawal. Cocaine has significant effects on central nervous system dopamine, serotonin, and norepinephrine receptors, as well as on the release of these neurotransmitters.¹⁸ Experiments with animals suggest that repeated doses of cocaine cause a progressively increasing sensitivity to the effects of cocaine on behavior, particularly hyperactivity and co-

caine-induced seizures. This increasing sensitivity of the central nervous system is called the "kindling effect."¹⁹⁻²¹

In our study, mothers using both cocaine and heroin demonstrated synergistic effects on abstinence scores when compared with cocaine or heroin use alone. Pinel and Van Ott²² reported that when a stimulant, such as cocaine, is used repeatedly in animals, an increased sensitivity of the central nervous system results. They found that withdrawal from a second drug is made more severe when combined with the stimulant. It seems reasonable to postulate that chronic intermittent exposure to cocaine might cause a long-lasting impact on the developing fetal brain, and that the addition of heroin might have a synergistic effect resulting in the type of abnormal behavior we observed in these infants. If the fetal brain has been adversely affected by these two drugs, then close follow-up for signs of developmental delay or increased risk for sudden infant death syndrome should be considered.

We defined growth retardation and microcephaly on the basis of the population that we saw during the study period, rather than according to the standard criteria of Lubchenco et al.²³ Because it is well known that life-style can influence a mother's health, we chose to compare our study infants with a population that was as similar as possi-

ble. The mean (\pm SD) birth weight of the infants in our no drugs control group (3.35 ± 0.47 kg) agrees closely with recently published data for a large group of infants born in California.²⁴ Had we defined growth retardation and microcephaly on the basis of the Lubchenco et al growth curves, the differences between the birth weights and head circumferences of the study and the control groups would also have been significant.

Seventeen percent of the newborns in the cocaine group had growth retardation. Twenty-seven percent of the newborns in the cocaine group were microcephalic. Infants in the cocaine history group were less likely to have growth retardation or to be microcephalic than were those born to mothers who had recently used cocaine. This may suggest that continued use of cocaine in the third trimester of pregnancy when the infant is in a phase of rapid growth is a cause of growth retardation. A similar finding has been reported in alcoholic mothers.²⁵

The increased incidence of newborns who were small for gestational age in the cocaine group and who were microcephalic among the cocaine and cocaine/heroin groups could be due to several factors. Cocaine is reported to be an appetite suppressant and may lead to decreased maternal energy intake.²⁶ Fetal growth disturbances could also have been caused by a direct vasoconstrictive effect of cocaine on the placenta.²⁷ Cocaine has been reported to cause placental vasoconstriction, resulting in reduced fetal blood flow and fetal hypoxia.²⁸ Since fetal growth is dependent on adequate placental blood flow, this could account for the growth retardation and microcephaly we noted.²⁹

Eighty-five percent of the mothers who admitted using cocaine reported using freebase (crack) cocaine. Freebase cocaine causes significantly more vasoconstriction than does intranasally ingested cocaine.^{30,31} This could account for the severity of the growth retardation and microcephaly we observed.

Cocaine abusers commonly use other drugs, such as tobacco or alcohol.² Alcohol consumption could play a role in the decreased intrauterine growth of the newborns in the cocaine group, because newborns with fetal alcohol syndrome

also have a small head circumference and a low birth weight.³² However, the urine drug test results in the cocaine group were negative for alcohol, as were most of the maternal histories. None of the infants studied had the typical features of fetal alcohol syndrome.³³ Maternal cigarette smoking can cause decreased intrauterine growth.³⁴ Our crack-abusing mothers reported that they often mixed tobacco and marijuana with their cocaine and smoked it in the form of a cigarette. Our finding of an 82% incidence of tobacco use in our cocaine-smoking mothers agrees closely with the findings of others.¹⁷ Marijuana was found in the urine in 20% of the mothers whose test results were positive for cocaine, which compares closely with a 29% incidence reported by MacGregor et al.¹³

Placental vasoconstriction could also account for the threefold increase in meconium staining of the amniotic fluid we noted in the cocaine group. Fetal hypoxia has been reported to cause meconium staining in infants of heroin abusers.⁶ We did not find a close correlation between our infants with meconium staining and maternal chorioamnionitis.

Infants exposed to either cocaine or heroin have a greater incidence of prematurity than the drug-free infant population.^{6,13} Although chorioamnionitis is a leading cause of prematurity,³⁵ we did not find an increased incidence of clinical chorioamnionitis in the drug-exposed mothers in our study. We did find a high incidence of prolonged rupture of membranes in the infants who tested positive for cocaine (80%) who were premature. Naeye et al⁸ found a 60% incidence of acute infection in mothers who abused heroin, most of whom delivered prematurely. Others have found an increased incidence of premature rupture of membranes in crack-smoking mothers.¹⁷ We did not examine all the placentas of the mothers in our study who used drugs. A closer inspection of the placenta of the mothers who used drugs and delivered either premature or small-for-gestational-age infants might show closer agreement between chorioamnionitis and adverse outcome in this population.

SUMMARY

We concluded that while signs of withdrawal after prenatal cocaine expo-

sure are usually mild, they occur in a significant number of infants. Prenatal cocaine exposure coupled with heroin exposure markedly increases an infant's chances of showing signs of abstinence. Maternal and infant urine screen results may be negative and abstinence symptoms still may be present in the infant. Prenatal cocaine exposure is also associated with a significantly increased risk of growth retardation, microcephaly, prematurity, and meconium staining of the amniotic fluid.

We recommend that both maternal and infant urine be tested when there is suspicion of maternal drug use during pregnancy. All cocaine-exposed infants should also be screened for exposure to heroin and other drugs. We recommend that infants exposed to drugs in utero should be evaluated for signs of withdrawal using a standardized scoring system. Finally, these infants should be followed up closely after discharge from the nursery, as growth retardation, microcephaly, and abnormal behavior may all be suggestive of potential long-term neurologic or developmental problems.

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Adolescents and Condoms

Associations of Beliefs With Intentions to Use

Susan M. Kegeles, PhD; Nancy E. Adler, PhD; Charles E. Irwin, Jr, MD

• Sexually active adolescents should use condoms to prevent the transmission of sexually transmitted diseases, including human immunodeficiency virus. This study examined, among male and female adolescents, which beliefs about condoms are associated with intentions to use them if they have coitus in the next year. Teenagers attending adolescent health clinics completed self-administered surveys. Although most adolescents knew that condoms prevent sexually transmitted diseases, an increasing belief in the preventive effects of condoms was not associated with an increased motivation to use them. Instead, other immediate, short-term consequences, such as the ease with which they can be used and discomfort associated with their use, were most strongly associated with adolescents' intentions to use condoms. To encourage condom use, messages from physicians and other health care professionals must focus on adolescents' beliefs that are most likely to encourage or inhibit use of condoms. Health considerations should not be the sole emphasis of such communications if the goal is to increase the use of condoms among sexually active adolescents.

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There are high rates of sexually transmitted diseases (STDs) among sexually active adolescents, including *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and syphilis.¹⁻⁵ Furthermore, although acquired immunodeficiency syndrome is currently uncom-

mon among adolescents,⁶ there is concern that sexually active teenagers also may be at risk for developing acquired immunodeficiency syndrome or acquiring human immunodeficiency virus infection because of their sexual practices and high rates of STDs.⁷⁻¹⁰

Research indicates that latex condoms, when used correctly, are effective in preventing the transmission of various STDs, including human immunodeficiency virus.¹¹⁻¹⁷ The Surgeon General and the Centers for Disease Control, Atlanta, Ga, have urged all people, including adolescents, to use condoms if they are having sexual intercourse outside of long-standing, established, mutually monogamous relationships.^{18,19} Therefore, physicians and health educators are asked to encourage adolescents to use condoms if the teenagers are having intercourse. Little is known about adolescents' beliefs about the consequences of using condoms, and it is not known what specific beliefs about condoms are associated with intentions to use them. Greater understanding of those beliefs that are associated with intentions to use or not use condoms is an important precursor to developing effective interventions to promote condom use among teenagers.¹⁹

This study examined the extent to which different beliefs about condoms are associated with adolescents' intentions to use or not use them. The Theory of Reasoned Action, which has been used successfully to describe contraceptive and family planning behaviors,²¹⁻²⁴ underlies this research and guided our selection of variables to study in this investigation. Other variables may also affect whether condoms are actually used, such as the individual's ability to get the partner to agree to the use of condoms and the availability of condoms

at the time of intercourse. However, because an individual's intention to use condoms is the most basic variable for subsequent behavior,^{21,22} it is a key focus for intervention.

Most health education messages urging the use of condoms, including communications from physicians, focus exclusively on health aspects. Therefore, it is of particular interest to determine whether adolescents' beliefs about the utility of condoms in protecting them from STDs is associated with their intentions to use condoms. It is also of interest to examine whether concerns about the efficacy of condoms in the prevention of pregnancy are associated with intentions to use them, since beliefs that condoms have high failure rates with respect to contraception might be a barrier to their use.

METHODS

These data were collected as part of a larger study of adolescent decision making regarding contraceptive use in heterosexual sex.²⁵ These surveys were administered from February 1984 to September 1985. Subjects were male and female adolescents aged 14 through 19 years who were coming to one of two adolescent health care clinics in San Francisco, Calif. One clinic was based in a large university medical center and the other was part of Kaiser Permanente.

All teenagers who attended the clinics when an interviewer was present and who met the inclusion criteria for the study were invited to participate. Inclusion criteria were English-speaking, single, not pregnant, and without a developmental disability or a major psychosocial problem. There were frequent delays at the clinics, and the majority of the adolescents who declined to participate in the study cited reluctance to stay for an additional hour beyond their medical appointment. We do not believe that this selection factor is likely to introduce systematic bias to the study findings.

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Table 1.—Consequences Rated by Respondents

1. Makes it easy to have sex on the spur of the moment
2. Makes me the one responsible for preventing pregnancy
3. Makes it seem that I am planning to have sex
4. Uncomfortable or painful to use
5. Protects me from venereal disease
6. Easy to use
7. Gives me guilt feelings
8. Decreases sexual pleasure because of feel, taste, or smell
9. Expensive
10. Natural
11. Immoral
12. Inconvenient
13. Clean
14. Used by a lot of people my age
15. Can be used without my partner or me having to see a physician
16. Can be used without my parents' knowledge
17. Keeps me (my partner) from getting pregnant
18. Requires me to have self-control
19. Requires my partner to have self-control
20. Affects my physical appearance
21. Has minor or immediate side effects on my health

The socioeconomic distribution of adolescents attending the clinics was determined by examining the method of payment for visits. At the university-based clinic, 40% of the reimbursement came from Medi-Cal (Medicaid), 30% from a clinical teaching subsidy (partial funding for the visit was provided by a university teaching fund and the remainder was provided by the patient or parent), and 30% from private insurance. The socioeconomic distribution at the health maintenance organization is essentially a middle-class population of adolescents whose parents are employed full time.

Prior to the current investigation, a pilot study was conducted with 60 male and female adolescents from the university-based clinic. In open-ended interviews, subjects were asked to identify the "good" and "bad" aspects of using several different contraceptive methods, including condoms. Responses were compiled and integrated with a list of beliefs about contraceptives culled from the literature.^{23,24,26} A list of 25 consequences was developed from this pilot research, 21 of which are relevant to condoms (Table 1). Subjects rated the likelihood that each consequence might occur if they (or their partner) were to use condoms, withdrawal, the pill, or a diaphragm if they were to have sex in the next year. Surveys were self-administered with same-sex interviewers present to answer questions.

Subjects rated each consequence on a seven-point Likert-type scale that ranged from *very unlikely* (−3) to *very likely* (3) to occur

if the individual (or the individual's partner) used condoms when they had intercourse. Intention to use condoms in the next year if they had intercourse was assessed on a seven-point Likert-type scale ranging from *definitely would not* (−3) to *definitely would* (3) use condoms.

RESULTS

We expected that in addition to beliefs about condoms, gender, ethnic/racial background, prior sexual experience, and prior use of condoms might also influence intentions to use condoms in the next year. To examine the association between beliefs about condoms and an intention to use them above and beyond these influences, the effects of prior sexual experience, prior use of condoms, and racial/ethnic background were controlled for through the use of multiple regression.

The following four-step multiple regression procedure was conducted for each belief: (1) intention was first regressed onto sexual activity, (2) prior condom use was entered next, (3) racial/ethnic background was entered as a set of "dummy" variables²⁷ (note that these three steps were identical for each belief item), and (4) the specific belief item was then entered and the semipartial correlation was examined for statistical significance.

The decision was made not to control for the effects of gender through this procedure, but instead to analyze male and female adolescents separately. The dynamics of condom use may differ greatly for the two genders, and this approach will yield information about which beliefs clinicians and health educators should address for male adolescents and female adolescents in general. Although it would be of interest to examine if the relationship between beliefs and intentions differs by race/ethnicity, our sample size within gender and race/ethnicity was too small to allow for the statistical analyses.

To reduce the type I error rate due to numerous statistical tests, only semipartial correlations that were significant at least at $P < .01$ were interpreted as significant and reported.

To determine the total amount of variation in intentions to use condoms that could be explained by the relevant beliefs, those beliefs found to be significantly related to intentions to use con-

doms were then simultaneously entered as a set into a multiple regression analysis. Beliefs were entered simultaneously because we considered it impossible to determine a priori which beliefs should be entered first in a hierarchical manner.

Only those consequences found to be significantly associated with intentions to use condoms were examined in detail, with the exception of beliefs about the efficacy of condoms to prevent STDs and pregnancy. It is of interest to determine the distribution of those beliefs found to be significantly related to intentions since such information can inform health care providers of which messages might be most effective.

Sample

The sample consisted of 345 female adolescents and 161 male adolescents; 32% (110) of the female adolescents and 43% (70) of the male adolescents were virgins. Of the sexually active adolescents, 59% (139) of the female adolescents and 63% (57) of the male adolescents had used condoms. The mean age of female adolescents was 16.7 years (SD, ± 1.36 years) and of male adolescents was 16.2 years (SD, ± 1.44 years). The ethnic/racial breakdown of the sample was as follows: 35% (179) were non-Hispanic white, 33% (167) were black, 13% (68) were Hispanic, 10% (51) were Asian, and 8% (41) were "other" (mixed or did not report). The educational level of the sample at the time of the study was as follows: 6% (29) were in seventh or eighth grade, 35% (179) were in ninth or 10th grade, 42% (215) were in 11th or 12th grade, 10% (49) were in college or junior college, 2% (11) had dropped out of school, 2% (9) were high school graduates and were not attending school, and 3% (14) did not provide this information.

Female Adolescents

Female adolescents who had not had intercourse were more likely than sexually active female adolescents to intend to use condoms in the next year if they were to have intercourse ($r = .28$, $P < .001$). This is consistent with previous research showing that condoms are frequently used early in one's sexual "career," before moving on to more effective prescriptive methods.^{28,29} Previous condom use, entered next in the

Table 2.—Semipartial Correlation Coefficients of Beliefs Associated With Intentions to Use Condoms, Controlling for Sexual Activity, Prior Condom Use, and Racial/Ethnic Background*

Beliefs	<i>r</i>	
	Female Adolescents	Male Adolescents
Condoms enable one to have sex on the spur of the moment	.17†	.28†
Condoms are easy to use	.14‡	.52†
Using condoms are popular with one's peers	.23†	.29†
Using condoms requires one's partner to have self-control	.17†	NS§
Condoms are clean	.18†	NS§
Condoms are inconvenient	-.19†	NS§
Condoms are painful or uncomfortable to use	NS§	-.31†
Using condoms makes the male adolescent responsible for contraception	NS§	.29†

*Semipartial correlation coefficients from individual multiple regression correlations between beliefs and intentions.

† $P < .001$.

‡ $P < .01$.

§NS indicates not significant.

Table 3.—Means, Confidence Intervals (CIs), and Distribution of Beliefs Associated With Intentions to Use Condoms in Female Adolescents

Beliefs	Mean* (95% CI)	% Endorsing†	
		Unlikely	Likely
Spur of the moment	0.90 (0.69, 1.11)	29.0	66.1
Easy to use	1.49 (1.30, 1.68)	15.9	79.5
Inconvenient	0.05 (-0.75, 0.27)	48.7	49.7
Clean	0.64 (0.42, 0.86)	34.2	59.7
Popular with peers	2.05 (1.88, 2.20)	9.2	86.7
Partner needs self-control	1.05 (0.82, 1.28)	25.1	69.0
Protects from venereal disease	1.51 (1.30, 1.72)	17.6	76.7
Can get pregnant	-0.70 (-0.52, -0.88)	62.7	3.6

*The response scale ranged from *very unlikely* (-3) to *very likely* (3) to occur if the individual's partner used condoms when they had intercourse.

†Percentages do not sum to 100 because neutral responses were deleted from the table.

multiple correlation procedure, also was significantly associated with intention to use condoms ($sr = .19$, $P < .001$); prior use was associated with a greater estimated likelihood of future use. Ethnic/racial background was not significantly associated with intentions to use condoms.

After controlling for the influence of sexual activity, prior experience with condoms, and racial/ethnic background,

the following five beliefs were found to be positively associated with intentions to use condoms: they enable one to have sex on the spur of the moment, they're easy to use, clean, popular with peers, and using them requires one's partner to have self-control (Table 2). In addition, considering condoms to be inconvenient was significantly associated with decreased intentions to use them. There was no significant association be-

tween intentions to use condoms and believing that they prevent STDs or that they are effective in preventing pregnancy.

The total R , including sexual activity, prior condom use, and the beliefs about condoms, was statistically significant, and thus showed these factors to be associated with intentions to use condoms among female adolescents ($R = .48$; $df = 8$, 304; $P < .001$). After controlling for the influence of sexual activity and prior condom use, the set of six beliefs explained a significant amount of variation in intentions to use condoms ($sr^2 = .13$, $P < .001$).

Means and 95% confidence intervals (CIs) for beliefs that are significantly associated with intentions are shown in Table 3. Beliefs about the consequences of using condoms were assessed on continuous scales, but for the purposes of descriptive analyses, the scales were collapsed in the following way: scores between 1 and 3 represent beliefs that the particular consequence is likely to occur by using condoms and scores between -1 and -3 indicate a belief that the consequence is unlikely to occur. A score of 0 indicates neutrality with respect to the likelihood that a given consequence will occur.

As shown in Table 3, the greatest consensus among female adolescents was that condoms are popular with their peers (87%), they prevent STDs (80%), and they are easy to use (80%). A majority (66%) believed that condoms enable one to have sex on the spur of the moment, are clean (60%), and require the male partner to use self-control (69%). On the issue of inconvenience, 50% believed condoms to be inconvenient. A sizeable minority of female adolescents (32%) believed it likely that one could get pregnant using condoms.

Male Adolescents

No significant association between sexual activity and intention to use condoms was found for male adolescents, indicating that those who had sex and those who did not differ significantly in their intentions to use condoms if they have sex in the next year. However, prior experience with condoms was associated with future intentions ($sr = .17$, $P < .05$), with male adolescents who used condoms more strongly in-

Table 4.—Means, Confidence Intervals (CIs), and Distribution of Beliefs Associated With Intentions to Use Condoms in Male Adolescents

Beliefs	Mean* (95% CI)	% Endorsing†	
		Unlikely	Likely
Spur of the moment	1.64 (1.39, 1.89)	12.5	82.4
Easy to use	1.85 (1.60, 2.10)	13.2	82.4
Makes me responsible for contraception	2.28 (2.09, 2.47)	4.5	93.1
Painful or uncomfortable	-0.71 (-1.04, -0.38)	58.0	35.4
Popular with peers	2.21 (1.99, 2.43)	6.6	92.7
Protects from venereal disease	2.23 (2.01, 2.45)	6.4	92.9
Can get partner pregnant	-1.69 (-1.93, -1.45)	82.7	10.9

*The response scale ranged from *very unlikely* (-3) to *very likely* (3) to occur if the individual's partner used condoms when they had intercourse.

†Percentages do not sum to 100 because neutral responses were deleted from the table.

tending to use them again than those who had never used them. Ethnic/racial background was not significantly associated with intentions to use condoms.

After controlling for the effects of sexual activity and previous experience with condoms, the following four beliefs were found to be positively associated with intentions to use condoms in the next year: they enable one to have sex on the spur of the moment, they make the male adolescent responsible for using contraception, they're easy to use, and they're popular with peers (Table 2). In addition, the belief that condoms are painful to use was associated with a decreased intention to use them. Among male adolescents, as was found with female adolescents, the intention to use condoms in the next year was not associated with believing that condoms prevent STDs or that condoms are effective in preventing pregnancy.

The total R , including sexual activity, prior condom use, and the four beliefs listed above was statistically significant, and thus showed these factors to be associated with intentions to use condoms among male adolescents ($R = .66$; $df = 7, 128$; $P < .001$). After controlling for the influence of sexual activity and prior condom use, the set of beliefs explained a significant amount of variation in intentions to use condoms ($sr^2 = .40$, $P < .001$).

In examining the means, CIs, and distribution of the beliefs found associated

with intentions to use condoms (Table 4), we found that the vast majority of male adolescents believed that condoms prevent the spread of STD (93%), are popular with their peers (93%), and that using them meant they were the ones responsible for not getting their partners pregnant (93%). Most also believed that condoms are easy to use (82%) and permit spontaneous sex (82%). A considerable minority believed it likely that condoms were painful or uncomfortable to use (35%) and that condoms would not protect against pregnancy (11%).

COMMENT

These data indicate that although most of the adolescents knew that condoms prevent STDs, belief in the preventive benefits of condoms was not associated with increased motivation to use them. Intervention programs aimed at increasing the use of condoms emphasize the effectiveness of condom use in the prevention of transmission of STDs (including acquired immunodeficiency syndrome). This sample appears to have understood this message from the prevention programs; however, it did not enter into consideration for using condoms. Contrary to our hypothesis, concerns about the possible efficacy or inefficacy of condoms in the prevention of pregnancy were also unrelated to intentions to use them.

These findings indicate that health and contraceptive considerations play a

minor role in the decision to use or not use condoms. Instead, a number of other immediate, short-term consequences were most strongly associated with adolescents' intentions to use condoms. Believing that condoms are easy to use and enable one to have spontaneous sex contributed to the intention to use them among both male and female adolescents. Likewise, for both sexes, believing that condom use is popular with peers encouraged their use. Many female adolescents were also motivated to have their partners use condoms because condoms are clean and because using condoms requires that the partner use self-control. The latter point may reflect a desire on the part of female adolescents that male adolescents participate in contraception and not leave the entire responsibility to them.

Interestingly, male adolescents appear to view such responsibility positively; the belief that using condoms makes them responsible for contraception was positively linked to an increased intention to use them. This "symmetry" between the male and female adolescents in their desire for the male adolescents to be more involved with the contraceptive process could provide an important focus of interventions with teenagers.

The primary barrier to using condoms among male adolescents appears to be the belief that condoms are painful, a belief shared by over one third of the sample. Several barriers to using condoms emerged among female adolescents. Nearly half believed condoms to be inconvenient to use. Many female adolescents also considered condoms not to be clean and felt that their use interferes with having spontaneous sex.

These findings suggest that physicians' communications to adolescents and the messages from public health and sex education programs, in addition to emphasizing the health aspects and disease prevention of condom use, must focus on the social and physical aspects of their use. Health considerations do not appear to be a salient dimension of the adolescents' choice to use or not use condoms. This may be particularly true if adolescents do not feel personally vulnerable to STDs and/or do not perceive STDs as a particularly severe health threat.

Since our goal is to encourage sexually active adolescents to use condoms, this study indicates that other positive aspects about condoms should also be emphasized in communications. Messages might focus on the positive aspects of using condoms, such as the shared responsibility for contraception that condom use entails and that rather than interfering with sex, condoms are easy to use, enable spontaneity, and are clean. It would also be of use to point out that many other teenagers also use condoms. To encourage condom use, messages need to take into account what the adolescents already believe, and focus on those beliefs most likely to serve as incentives. Clearly, not all beliefs about condoms are negative. To increase their use among those teenagers who are already sexually active and to reduce the spread of STDs, we must address the concerns that may inhibit their use and emphasize the incentives for use.

Our results also demonstrate that

there continue to be some misconceptions about condoms. Nearly 20% of female adolescents and 7% of male adolescents still do not understand that condoms prevent the transmission of STDs. In addition, some male adolescents believe that condoms are painful. Such misperceptions should be clarified (perhaps including advice to try different brands of condoms that may vary in fit), in addition to conveying the positive messages.

This sample was diverse with respect to socioeconomic status, educational level, and ethnic/racial background and may be quite representative of the kinds of adolescent patients health care providers are likely to see. A higher proportion of female adolescents in this sample were sexually active than male adolescents, as would be expected from a clinic sample, since female adolescents tend more often to seek health care for issues concerning sexuality and reproductive health (contraception or preg-

nancy testing) than do male adolescents. The extent to which the findings from this clinic are generalizable to adolescents not attending health care clinics is not known.

Many female adolescents attending clinics may be seeking to obtain prescriptive methods, including oral contraceptives, and do not intend to use condoms since they are contraceptively protected. Clinicians need to encourage adolescents to continue to use condoms or add condoms to their sexual practices as they initiate prescriptive methods.

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Comparison of Amoxicillin and Clavulanic Acid (Augmentin) for the Treatment of Nonbullous Impetigo

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• We undertook a prospective double-blind controlled study to compare the efficacy of a drug that usually has no antistaphylococcal activity (amoxicillin trihydrate) with the efficacy of the same drug with an addition of a β -lactamase inhibitor (amoxicillin plus clavulanic acid [Augmentin]) in the treatment of nonbullous impetigo. Fifty-one culture-positive patients, aged 6 months to 9 years, were included, 26 in the amoxicillin group and 25 in the Augmentin group. The study groups were clinically and bacteriologically comparable at the start of the study. *Staphylococcus aureus* was isolated from all patients and β -hemolytic streptococcus from 14 (29%). All staphylococci were sensitive to Augmentin but resistant to amoxicillin. Forty-nine patients completed the study. The clinical response was significantly better among the Augmentin recipients (marked improvement in 71% and 95% of patients after 2 and 5 days, respectively; no new lesions during the treatment course) than among the amoxicillin recipients (marked improvement in 44% and 68% of patients after 2 and 5 days, respectively; new lesions appeared in 20% of patients). Recurrence within 3 weeks occurred in 12 (26%) of 49 patients, and no difference was observed between the two groups. We conclude that *S aureus* is common in nonbullous impetigo, and that at least in some cases it plays an important role in the course of the disease that can be altered by specific therapy.

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The role of systemically administered antibiotics in the treatment of impetigo is well established. This mode of treatment is usually superior to local treatment.¹⁻⁴ However, controversies still exist over the optimal systemic anti-

biotic to be used. It is well established that *Staphylococcus aureus* can be isolated from a substantial number of impetiginous lesions, either as a single pathogen or in conjunction with streptococci.^{1-3,5-8} However, its causative role and hence the necessity to administer penicillinase-resistant drugs is still debated. While *S aureus* has been regarded as a "secondary offender" by many authorities who claim that it plays no important role in the disease,⁹⁻¹⁴ others believe that *S aureus* is important and may even be the sole infecting organism in this type of skin infection.^{7,8,15}

We therefore undertook a prospective double-blind controlled study to compare the efficacy of a drug, which in our community usually has no antistaphylococcal activity (amoxicillin trihydrate), with the efficacy of the same drug with an addition of a β -lactamase inhibitor (amoxicillin plus clavulanic acid [Augmentin]) in the treatment of nonbullous impetigo.

PATIENTS AND METHODS

We included in the study infants and children under 13 years of age presenting with nonbullous impetigo at two pediatric clinics in the Negev region of Israel, from May 15 to October 31, 1987. These clinics generally serve a population with crowded households that belong to lower social middle classes.

The following data were recorded before the initiation of treatment: patient age, the presence of fever (temperature $\geq 38^{\circ}\text{C}$), number of lesions, diameter of the three largest lesions, and the presence of regional lymphadenopathy.

The three largest lesions were cultured as follows: The corner of the crust was lifted to reach the fresh exudate underneath. The lesion was then touched by a sterile cotton swab and immediately streaked onto a 5% sheep blood agar plate, which was transferred to the clinical bacteriology laboratory in Soroka Medical Center, Beer Sheva, Israel, on the same day. Concomitantly, a second

set of cultures was transferred to the laboratory in a transport medium (Culturette, Marion Scientific, Kansas City, Mo).

After obtaining the cultures, patients were randomized to receive either amoxicillin trihydrate syrup (40 mg/kg per day, three times a day) or amoxicillin/clavulanic acid (Augmentin) syrup (40 mg/kg per day of amoxicillin trihydrate and 10 mg/kg per day of clavulanic acid, three times a day) in a double-blind fashion.

The patients were followed up on days 2, 5, and 10 and evaluated for (1) the morphologic structure of the lesions (on day 2, the grades were markedly improved, slightly improved, or not improved; on days 5 and 10, the grades were cured, markedly improved, slightly improved, or not improved), and (2) the appearance of new lesions.

The definitions for improvement were as follows: cured, lesions disappeared or were completely dry; improved, lesions were less extensive or some were dry, but at least some were still not completely dry; and not improved, lesions were as before treatment or worse. In addition, on days 2 and 5, the physician had to decide whether a repeated culture was needed (given that the lesion was not completely dry).

Compliance was assessed by the amount of drugs left in the bottles at each visit. The patient was contacted by telephone again after 3 weeks to determine the recurrence rate of the infection. If impetigo recurred (as defined by new lesions), the patient was seen in the clinic and treated with cephalixin.

Bacteria and Sensitivity

The presence of group A streptococcus was screened by bacitracin disk (0.04 U) after incubation in 5% carbon dioxide for 18 to 24 hours. Confirmation was performed using specific serotyping (Wellcome Diagnostics, Dartford, England).

Identification of *S aureus* was based on colony structure, pigment, and hemolysin production. Confirmation was performed by the slide coagulase technique. Antibiotic susceptibility was performed by the method described by Bauer et al.¹⁶ Statistical analysis was performed by Fisher's Exact Test. $P < .05$ was considered significant.

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RESULTS

During the study period, 52 patients were enrolled. Culture was positive in 51 patients who constituted the study group, 26 in the amoxicillin group and 25 in the Augmentin group. The two study groups were not significantly different in their age, distribution, the presence of fever, number and diameter of the lesions, the presence of regional lymphadenopathy, and culture results (Table 1).

Staphylococcus aureus was isolated from all 51 patients with positive culture. From 14 (29%) of 51 patients, a β -hemolytic streptococcus was also isolated: group A streptococcus from 11, group G streptococcus from 2, and

group B streptococcus from 1. All streptococci were sensitive to both amoxicillin and Augmentin. All staphylococci were resistant to penicillin and amoxicillin, but sensitive to Augmentin. In 16 (32%) of the 51 patients with staphylococci isolated, organisms were resistant to erythromycin. Two patients were dropped from the study after initiation of treatment: one in the Augmentin group was unavailable for follow-up, and another in the amoxicillin group developed severe side effects. All other patients completed the 10-day course and were judged to be compliant. Side effects were noted in 2 (8%) of 26 patients in the amoxicillin group (vomiting in 1 patient and diarrhea in the other). Side effects were not noted in any of the

25 Augmentin recipients.

The course of the disease after initiation of treatment in the 49 patients who were available for follow-up is presented in Table 2. It is clearly seen that the rate of clinical improvement and cure rates were markedly higher in the Augmentin group than in the amoxicillin group. Furthermore, 20% of patients in the amoxicillin group developed new lesions during treatment vs 0% in the Augmentin group. Twenty-four percent of the patients in the amoxicillin group were still culture-positive after 5 days of treatment vs only 4% in the Augmentin group. All positive lesions after initiation of therapy yielded *S aureus*.

Impetigo recurred within 3 weeks in 12 (26%) of 49 patients—6 of 25 patients in the amoxicillin group and 6 of 24 in the Augmentin group.

COMMENT

We have shown in the present study that *S aureus* is present in most cases of nonbullous impetigo in our region and that systemic treatment with a drug with an antimicrobial spectrum that includes *S aureus* is indicated in such an epidemiological setting.

For many years, impetigo had been considered a streptococcal disease.⁹⁻¹⁴ However, *S aureus* has been constantly isolated in a high proportion of impetiginous lesions, and in several recent studies, it was present in over 90% of the cases while *Streptococcus pyogenes* was isolated in about one of three of the cases, usually together with *S aureus*.^{7,17} In fact, a review of 17 studies

Table 1.—Comparison Between Children With Impetigo Assigned to Amoxicillin or Clavulanic Acid (Augmentin) Treatment

Variable	Amoxicillin Group (N=26)	Augmentin Group (N=25)
Age, mo		
Range	6-108	7-90
Mean \pm SD	34.7 \pm 25.0	38.8 \pm 25.8
No. (%) of children with a temperature $\geq 38^\circ\text{C}$	2 (8)	0
No. of lesions		
Range	1- ≥ 10	1- ≥ 10
Mean \pm SD	4.2 \pm 3.4	5.0 \pm 3.8
Larger-diameter lesions, cm		
Range	5-16	5-35
Mean \pm SD	1.0 \pm 0.4	1.2 \pm 0.7
No. (%) of children with regional lymphadenopathy	8 (32)*	13 (54)*
No. (%) of children with positive cultures β -hemolytic streptococci	7 (27)	7 (29)
<i>Staphylococcus aureus</i>	26 (100)	25 (100)

* $P > .05$.

Table 2.—The Course of Impetigo After Initiation of Treatment in 25 Patients Who Received Amoxicillin and 24 Patients Who Received Clavulanic Acid (Augmentin)

Variable	No./Total (%) of Patients					
	After 2 D		After 5 D		After 10 D	
	Amoxicillin	Augmentin	Amoxicillin	Augmentin	Amoxicillin	Augmentin
Markedly improved or cured	11/25 (44)	17/24 (71)	15/22 (68)*	21/22 (95)*	20/25 (80)	23/24 (96)
Patients with new lesions	5/25 (20)	2/24 (8)	5/22 (23)†	0/22 (0)†	5/25 (20)*	0/24 (0)*
Patients in whom cultures were judged "indicated"	13/25 (52)	8/23 (35)	9/22 (41)†	1/22 (4.5)†
Positive cultures	9	5	6	1

* $P < .05$ between amoxicillin and Augmentin groups.

† $P < .01$ between amoxicillin and Augmentin groups.

from Europe and the United States revealed that in less than 35% of the cases streptococcus was the sole isolated organism. In contrast, in 16 of 17 studies *S aureus* was isolated alone or with streptococcus from 65% to 98% of the cases.⁷ Furthermore, it was previously shown that lesion morphologic study could not accurately determine whether a particular patient had streptococcal or staphylococcal pyoderma and that *S aureus* predominated in all four morphological forms of impetigo (vesicular, bullous, pustular, ecthymatous, and erosive).^{7,11,14} The facts reviewed above suggested that there is an overall change in the origin of impetigo and that at the present time *S aureus* is becoming dominant, causing lesions that cannot be differentiated from those caused by group A streptococcus. Therefore,

several authors have claimed that drugs with activity against both streptococci and staphylococci should be considered in impetigo.^{7,8,14} To the best of our knowledge, our study is the first to blindly compare a regimen active against both staphylococci and streptococci vs a regimen active against streptococci only.

It may well be that impetigo is still primarily a streptococcal disease and that staphylococci are indeed secondary invaders, maybe playing only a minor role in the pathogenicity. Contributory to this opinion is the fact that a marked improvement as early as after 2 days was observed in 44% of the amoxicillin-treated patients, with a total cure rate of 80%, despite the uniform presence of staphylococcus. However, our results suggest that, at least in some cases, staphylococci do play an important role

in the course of the disease that can be altered by specific therapy.

It is interesting that the recurrence rate within 3 weeks was similar in the two treatment groups. This suggests a reinfection rather than a partially treated situation.

We conclude that in areas where *S aureus* is usually penicillin resistant, the empiric therapy of impetigo should include a drug that is active against both staphylococci and streptococci. In view of recent success with a new topical drug active against both streptococci and staphylococci, namely, mupirocin,¹⁷⁻¹⁹ the role of appropriate topical drugs should be assessed.

Statistical analyses were performed by Lily Neuman, PhD, from the Clinical Epidemiology Unit, The Ben-Gurion University of the Negev.

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In Other AMA Journals

ARCHIVES OF SURGERY

Medullary Carcinoma in Children: Results of Early Detection and Surgery

Robert L. Terlander, MD; Donald Zimmerman, MD; Glen W. Sizemore, MD; Jon A. van Heerden, MB, ChB; Clive S. Grant, MD (*Arch Surg*. 1989;124:841-843)

A Model to Determine the Feasibility of a Pediatric Practice

Kimball A. Miller, MD, MSHA; Deborah A. Miller, MS; Gerald A. Doeksen, PhD; Patti Jacobs

• A major concern of urban and rural citizens of the United States is the availability of adequate pediatric health care in their community. Community leaders attempting to recruit health care providers and pediatricians considering locating their practice in a specific community need a method by which they can evaluate a community's potential for supporting a new primary care practice. A detailed survey was conducted in early 1988 of pediatric practices geographically dispersed throughout the state of Oklahoma. Data collected from the physicians and their administrative staff reflected the volume of office and hospital visits and practice costs over the prior 12 months. Using the capital costs and direct operating cost data with information obtained on the number of patient visits and revenue generated collected in this survey, we designed a model to project the economic feasibility of establishing a pediatric practice in a specific community. This model can be used to project the number of annual pediatric primary care visits a community can generate, the direct and indirect costs to establish and maintain a clinic, and the gross revenue and net income of the practice.

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Pediatricians are being solicited by community leaders and health care administrators of many small and me-

each of their location options with regard to the potential survival and growth of a new primary care pediatric practice. To this end, pediatric residents completing training and community leaders in Oklahoma have sought assistance from agencies experienced in physician placement, health care design, and economics to help them determine a nonmetropolitan community's ability to support a primary care physician. To achieve this goal, personnel from the Oklahoma state universities and medical schools have worked together to design a model to be used with prospective pediatricians and community leaders for estimating a community's patient primary care needs and the economic feasibility of a practice. Our objective is to explain the research method and the model derived from a survey of geographically diverse, established pediatric practices.

Various publications have previously outlined several necessary steps in selecting a site for a medical practice. Researchers such as Balliett¹ have suggested selecting a practice site by investigating a selected population's income levels, projected changes in an area's population, and the historical ability of the members of the community to pay for medical services. Donohugh² advises consulting a table illustrating the population-to-physician ratios for specific specialties to determine the area's needs and a comparison to national norms. Cotton³ suggests using a location scoring method taking into consideration such factors as local and regional medical facilities, community economic background and growth, and stable community resources that include public schools, recreation facilities, and housing. Furthermore, the recommended guidelines of the American Academy of Pediatrics, Elk Grove Village, Ill, in terms of the population required to support a pediatrician, suggest that one physician is needed per 2500 children

less than 18 years old.⁴

The need for developing an economic model for analyzing practice sites in nonmetropolitan Oklahoma communities was first identified by Doeksen and colleagues,⁵ who investigated the costs of establishing a community clinic. In 1983 Williams and colleagues⁶ collected basic financial data from 16 primary care physicians through the use of structured interviews. This model was later expanded to include the observations of 25 primary care physicians in 1987, which then formed the database to allow a physician, community leader, or other health professional to evaluate the economic feasibility of a potential practice site.⁷

SURVEY METHODS

Recognizing a need to modify this 1987 primary care provider model to take into consideration the unique practice requirements of pediatricians, we designed a pediatric care model and conducted structured interviews with Oklahoma pediatricians and their administrative staff in the spring of 1988.

The pediatricians surveyed geographically represented all areas of the state and were selected to include new pediatricians (in practice <2 years) and established pediatricians. Based on these criteria, the research team selected 10 pediatricians practicing in Oklahoma, all of whom completed the interviews and data collection forms.

Of the 10 surveyed physicians, 5 were in solo practices, 3 were in partnerships, and 2 were in a multispecialty group or association. Seven had been in practice more than 2 years. All were located in nonmetropolitan communities of less than 100 000 population as follows: 2 in communities of less than 5000, 4 in communities between 25 000 and 50 000, and 1 in a city of more than 50 000. The extensive survey questionnaires were administered personally by members of the research team to each physician and designated practice administrator.

To develop a model that could determine a community's ability to support a pediatrician or an additional pediatrician, we needed information on the number of pediatric pri-

See also p 924.

dium-sized communities to set up practices in their communities. To make an informed decision, they must evaluate

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mary care visits a practice area will generate, the average number of annual pediatric visits per provider, the capital and operating expenses of a practice, and a projection of gross revenue and net income generated by a specific number of primary care visits.

Primary Care Visits per Practice Area and Physician

Although information on the frequency of visits to physicians and the number of office visits per year categorized by patient age and sex was not available specifically for Oklahoma, national rates were available from a national survey of ambulatory care conducted by the US National Center for Health Statistics, Washington, DC.⁸ The national data were used to determine the number of visits that would be expected from a community or geographic practice area (Table 1).

To obtain data regarding the average number of visits per primary care provider, specific Oklahoma data were obtained using the above survey method. The case study of the 25 family practice physicians conducted in 1987 and the present study of 10 pediatric physicians provided information on the number of office visits, hospital visits, and nursery visits for physicians providing pediatric health care.

Based on observations of the seven established pediatric office practices, the average number of annual pediatric office visits per physician was 5163. This number approximates the published national norm of visits to pediatricians in nonmetropolitan areas, which is 5177.⁸ While the established pediatrician will average 430 monthly visits, the average for a new pediatrician did not approach this level. The average number of monthly visits for the three new pediatricians was 60 for the first month, 119 for the fourth month, and 203 for the seventh month. Of special interest is the range of visits for each month. In every case, the highest number for every month was at least three times that of the lowest number, which illustrates the wide variation in the number of patient visits individual beginning pediatricians will most likely experience. Furthermore, new pediatricians in solo practice seem to have fewer visits during the early months of practice than new pediatricians joining a group practice.

The number of office, hospital, emergency department, nursery, and after-hours clinic visits were averaged for the new and established pediatricians. Furthermore, because of the different types of visits and rates of reimbursement, office visits were subdivided as initial (new patients) or routine (regular patients/follow-up visits). Even though some physicians may choose to limit the number of new patients, we determined in this study that an average of 15% of a physician's

Table 1.—Number of Primary Care Visits by Gender per 100 Population, United States, 1981*

Age Group, y	Male Patients†	Female Patients†	Weighted Average†
<1	669.1	611.2	640.8
1	385.4	361.4	373.9
2-5	232.6	206.3	219.6
6-10	184.0	173.5	178.8
11-14	105.5	99.5	102.5

*Adapted from National Center for Health Statistics data.⁸

†Calculated by dividing the number of office visits to pediatricians by the percent seen by a pediatrician.

Table 2.—Average Number and Range of Annual Pediatric Office, Hospital, Emergency Department, Nursery, and After-Hours Clinic Visits for Oklahoma Pediatricians, 1988

Type of Visit	No. of Observations	Average	Range	
			Low	High
Office	7	5163	3937	6500
Emergency department	6	146	50	500
Hospital	6	176	50	439
Nursery	6	303	0	800
After-hours clinic	6	120	0	600
Total Encounters	...	5908	4037	8839

office practice consisted of initial visits. Data from the survey determined that 3.4% of the physician office visits would give an estimate of the number of hospital visits. Likewise, 2.8% of office visits yields an estimate of emergency department visits, and 5.8% of office visits estimates nursery visits. Additionally, the survey data indicate that pediatricians can expect that 5% of their office visits will result in roentgenogram charges if the practice has roentgenogram facilities, and 43% of total office visits produced patient fees (laboratory or office procedures) in addition to the standard fee for the office visit. Therefore, as illustrated in Table 2, the typical surveyed pediatrician annually had 5908 patient encounters with a range from 4037 to 8839.

Capital and Operating Expenses

To obtain data on practice capital costs, a complete inventory of all furniture and equipment found in each office (business office, laboratory, examination rooms, reception room, conference room, and physician's office) was completed by a research team member. If the physician knew the cost of the equipment, that information was included. In other cases, however, dealers of capital equipment were interviewed to obtain an average cost of each item found in the practice. With regard to physical plant cost, the physician provided either construction costs with

specific loan terms or annual rental payment data. Furthermore, to develop the database concerning operating costs, four aspects of the practice (personnel, building, office, and medical costs) were evaluated. Personnel costs included wage and benefits for professional and support staff; insurance, taxes, utilities, and maintenance comprised the building costs; office expenses were those associated with the business office operations, professional expenses, and malpractice insurance; and medical costs referred to laboratory and medical supplies used in the provision of patient care.

Regarding the second category of survey research data, capital and operating costs, the survey indicated that a solo pediatrician utilized approximately 1300 to 1600 sq ft of space. The data also indicate that space requirements varied with the number of providers within a practice. For example, approximately 900 sq ft of additional space is needed for a third member. Depending on the clinic, this may include examination rooms, business office, reception areas, laboratory, and conference areas. To arrive at an average for capital costs, survey information from both the 1987 and 1988 studies was used. The surveyed physicians, for whom there was accurate data, had an average of \$97 500 invested in buildings, \$11 000 in land, and \$25 762 in equipment. For practices that rented space, the monthly charges varied

from \$100 to \$2200 depending on the lease (Table 3). As for operating costs, information on the building, office, personnel and medical supply costs was obtained from the pediatric physicians. Their average annual operating cost was \$76 276 per provider (Table 4). These figures reflect costs in nonmetropolitan parts of the Midwest and would have to be adjusted for different parts of the country.

Gross Revenue and Net Income

The gross revenue data were obtained by documenting the amount charged for specific types of visits, procedures (ie, roentgenograms, injections), and laboratory services. The amounts were then modified to reflect current collection rate and third-party payer reimbursement plans.¹⁰ The average, low, and high fees charged for 16 of the most common types of services were tabulated (Table 5). These charges were then multiplied by the number of visits in each category and modified using information on collection rates that were obtained from the physicians. The determination of net income was derived by subtraction of annual operating costs and capital cost from the gross revenue modified by collection rates.

MODEL

Based on the data from the 1987 and 1988 studies, we designed a model for physicians and community leaders to use in determining the economic feasibility of establishing a pediatric practice in an area. The basic parts of the model are (1) a procedure to estimate the annual number of pediatric primary care physician visits and number of providers needed in the service area, (2) a procedure to estimate operating and capital costs for provider (capital costs are converted to annual costs by assuming that the physician takes a loan and pays principal and interest charges), (3) a method to project gross revenue modified for collection rates, and (4) a determination of net provider income.

The model has been developed as a series of 11 forms with 17 pages of explanation to help the user complete the feasibility study. We will illustrate the model by discussing in detail the procedure to estimate the number of primary care physician visits and providers needed in a service area, but other parts of the model will be summarized.

The first step in determining potential demand for primary care physician services in a community is to estimate the number of local office visits for all types of physicians. National survey data give the number of predicted office visits to the provider by gender per 100 population (Table 1). Applying this data, female patients who are 1 year of age would generate a total of 360 per 100 or 3.6 office visits per year. Table 6 includes the utilization rates for all the gender and age

Table 3.—Monthly Rents per Primary Care Clinic Facility in Oklahoma, 1988*

Facility	Average	Range	
		Low	High
All observations	887	100	2200
Community-owned office complex			
Facility bills paid	665	200	1685
Facility bills not paid	325	100	550
Privately owned office complex			
Facility bills paid	1037	500	220
Facility bills not paid	920	300	1910

*Values are in US dollars.

Table 4.—Average Annual Operating Costs per Pediatrician*

	Average	Range	
		Low	High
Building costs (utilities, maintenance, taxes, and insurance)	6971	2281	17 586
Office costs (telephone, office supplies, billing, automobile expenses, and professional dues)	21 686	4990	40 595
Medical costs (equipment maintenance, medical supplies, and malpractice insurance)	19 090	6121	39 753
Personnel costs (assume licensed practical nurse and receptionist/bookkeeper only)	28 529	20 644	41 055
Total	76 276	34 036	138 989

*Values are in US dollars.

Table 5.—Representative Rates Charged by Oklahoma Pediatricians for Major Categories of Services, 1988*

Type of Source	Average	Low	High
Office visits			
Initial	35	26	55
Routine	25	20	35
Follow-up	20	10	30
Well-child care	26	20	35
Counseling	40	35	50
After hours/weekends	39	25	50
Hospital			
Admission	89	55	150
Visit	32	20	60
Nursery care†	117	80	140
Intensive care unit admission	137	75	220
Emergency department visit	46	35	60
Other			
Complete pelvic examination	36	25	50
Roentgenogram	32	25	40
Laceration repair	38	30	50
Nurse visit	14	12	16
Home visit	52	45	60

*Values are in US dollars.

†This includes nursery admission and 2 days of nursery visits.

Table 6.—Estimated Number of Annual Primary Care Office Visits by Age and Gender for Service Area

Age Group, y	Male Patients				Female Patients				Area Total Visits
	Utilization Rate		Population	Total Visits	Utilization Rate		Population	Total Visits	
<1	6.7	×	88	= 590	6.1	×	96	= 586	1176
1	3.9	×	79	= 308	3.6	×	78	= 281	589
2-5	2.3	×	309	= 711	2.1	×	277	= 582	1293
6-10	1.8	×	380	= 684	1.7	×	381	= 648	1332
11-14	1.1	×	282	= 310	1.0	×	276	= 276	586
Total				2603				2373	4976

categories in a pediatric practice for a theoretical small community and serves as an illustration of how an estimation of the primary care office visits is generated. To derive this information, one would determine the service area of the community and estimate its population using community census data. These data are available from state and local agencies.

Examples of agencies providing this information at the local level include Chamber of Commerce, community school district office, area planning agency, county medical society, and community hospital administrative staff. State resources of information include state and private medical schools, universities, and economic development agencies. The service area is determined by identifying the location of physicians in surrounding communities. If the communities are the same size, it is assumed that the service area extends halfway between the communities. If the communities are larger, it is assumed that the larger communities have a larger service area based on population size. For example, if one is twice as large as the other, the service area extends twice as far. In addition, local conditions, such as geographic boundaries, transportation capabilities, and the type and number of providers in the surrounding communities, are also used if they warrant consideration.

After the total population of the service area has been categorized by age and gender, the user multiplies the group totals by the utilization rates from the national survey.⁸ This same procedure is continued for each service category, and the total number of physician visits is calculated. According to the national ambulatory care study,⁸ when visits to the four primary care specialties (family practice, internal medicine, pediatrics, and obstetrics and gynecology) are totaled, 71% to 91% of all office visits are handled by these physicians (Table 7).

Once the potential number of local primary care office visits is estimated, a method is needed to determine the number of pediatricians that can be supported in the area (Table

Table 7.—Percent Distribution of Office Visits by Physician Specialty, by Selected Ages of Patients, United States, 1980 to 1981*

Physician Specialty	Patient Ages, y		
	<2	2-5	6-14
General and family practices	20.9	23.0	28.2
Pediatrics	68.9	60.5	40.0
Obstetrics and gynecology	0.5	0.2	0.5
General surgery	1.5	1.8	2.7
Internal medicine	0.7	1.0	2.2
Orthopedic surgery	1.5	1.7	5.2
Ophthalmology	0.8	2.0	5.0
Otolaryngology	1.4	4.1	3.7
Dermatology	0.6	1.5	4.6
Psychiatry	0.3	0.3	1.5
Other	2.9	3.9	6.4
Total	100.0	100.0	100.0

Adapted from National Center for Health Statistics data.

Table 8.—Estimated Number of Pediatricians an Area Can Support

1. Estimated total office visits for local area (from Table 6)	4976
2. Office visits to physicians or pediatricians already practicing in area (if unknown, calculate as follows: No. of full-time equivalent pediatricians × 5163 office visits + No. of full-time general and family physicians × 0.22 × 4600 office visits)*	0
3. Remaining potential office visits in service area (item 1 - item 2)	4976
4. Average No. of office visits per pediatrician (research determines this to be 5163)	5163
5. No. of additional pediatricians area could theoretically support (item 3/item 4)	0.96

*Data indicate that 22% of the primary care visits for children under age 14 years go to general and family physicians.

8). To do this, the average annual number of office visits for established pediatricians is used in the determination. Data from a national study conducted in 1985 show the average number of office visits per year was 5177, which was confirmed by the 1988 Oklahoma pediatrician study. To determine the number of pediatricians an area can support, the number of local office visits must be generated and modified by consideration of the number of family practice physicians and other primary care providers. This number

of office visits is then divided by the annual average number of visits per pediatrician to determine an estimate of the number of pediatricians that an area can support.

In the second part of the model, the user estimates all costs associated with the practice. The forms will estimate annual capital costs, principal and interest, and all operating costs by department (personnel, building, office, and medical).

The third part of the model uses the number of visits estimated and data on numbers

Table 9.—Estimated Number of Pediatric Visits by Service Category*

Category of Service	No. of Visits
Initial office visits 0.149 × 4976 total office visits	741
Routine office visits 0.851 × 4976 total office visits	4235
Visits with additional charges (not roentgenogram) 0.43 × 4976 total office visits	2140
Visits with roentgenogram charges If no roentgenogram facilities, proceed to next item Clinic with roentgenogram facilities 0.05 × 4976 total office visits	249
Hospital visits 0.034 × 4976 total office visits	169
Emergency department visits 0.028 × 4976 total office visits	139
Nursery room visits 0.058 × 4976 total office visits	289
After-hours clinic visits 0.023 × 4976 total office visits	114

*Total office visits should be taken from Table 6 or, if more than one physician can be supported, the average of 5163 visits.

of different service categories of visits to project the total number of outpatient and inpatient visits generated in the community (Table 9). These results are multiplied by alternative charge rates to estimate total fees charged. The model uses the survey average, high, and low charge rates, modified to reflect, if known, the usual and customary charges in the community. The user assumes a collection rate to estimate gross income, which can be obtained by visiting local physicians, community hospital administrators,

and business managers in the area. If no physicians are available, the model allows for default collection rates. Subtracting the estimated annual capital and operating costs from the estimated gross income yields an estimate of net income per pediatrician.

COMMENT

Using the model described here and information on the composition of the medical community, a user can project

the economic feasibility of establishing a pediatric practice in a specific nonmetropolitan community. Such information is valuable for pediatricians who are considering relocating their practices or residents who are considering beginning a practice. This model also helps community and hospital leaders who wish to recruit a pediatrician because it provides both parties with objective data. Since the first model was completed in early 1986, more than 50 such studies have been done at Oklahoma State University, Stillwater, and the University of Oklahoma College of Medicine, Tulsa. Residents completing their pediatric and family practice training at the University of Oklahoma Health Science Center-Tulsa, are taught to use the model when they are deciding on their medical practice site. Guidebooks were written to give detailed results of the 1987 family practice and 1988 pediatric surveys, and a computer program has been designed to aid users in completing a feasibility study.⁷ Residents who have used this feasibility model to choose practice sites are being monitored over time to determine the practicality of this modeling method and to offer suggestions of modifications for future revisions.

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ARCHIVES OF SURGERY

Changing Patterns of Treatment and Survival in Neonates With Meconium Ileus

Frederick J. Rescoria, MD; Jay L. Grosfeld, MD; Karen J. West, MD; Dennis W. Vane, MD (*Arch Surg*. 1989;124:837-840)

The Pediatric Marketplace

Gilbert A. Martinez, Alan S. Ryan, PhD

• This study presents an overview of the demography of office-based pediatricians, trends in the patient population, and the growth of the pediatricians' market share of children seeking primary medical care. The following four factors bear directly on the present and future status of the office-based pediatric practice: (1) size of the office-based pediatrician population, (2) size of the pediatric patient population, (3) the frequency of patient visits, and (4) the pediatric market share. Results indicate that the pediatricians' market share of young children has continued to grow. However, the pediatricians' share of young children has not grown fast enough to offset an increase in the pediatrician population. Continued growth of the pediatric practice may depend on developing effective marketing strategies and providing more primary care to the adolescent population.

(AJDC. 1989;143:924-928)

Several studies have centered on the future of pediatrics and the future scope of the pediatric practice.¹⁻⁴ Many of these findings, presented as editorials, describe the issues that must be addressed to meet the needs of the future pediatrician to ensure their place in a changing health care system. In the interest of providing the pediatric community with information concerning the

See also p 919.

status of pediatric practice, we briefly describe trends in the demography of the pediatrician and patient populations together with trends in the pediatricians' market share of the patient population, yielding a description of where pediatricians have increased their share of the patient population seeking primary medical care. We also consider important marketing issues that bear on the future of the pediatric practice.

Accepted for publication January 8, 1989.

From Ross Laboratories, Columbus, Ohio.

Reprint requests to Marketing Research, Ross Laboratories, 625 Cleveland Ave, Columbus, OH 43216 (Mr Martinez).

MATERIALS AND METHODS

Data used in this study were derived from three separate sources. Each is briefly described below.

Pediatrician Population Characteristics

Since the establishment of the Physician Masterfile⁵ in 1906, the American Medical Association (AMA) has been the principal source of information concerning the location, specialty, and activities of physicians. The Physician Masterfile contains current and historical descriptive data on all physicians in the United States and its possessions. The masterfile includes members and nonmembers of the AMA, and those who were and were not certified by their corresponding specialty board. The *Physician Characteristics and Distribution in the US*,⁶ published yearly, summarizes the data compiled in the masterfile.

A file is started on each individual on entry into medical school, or in the case of foreign or Canadian medical graduates, on entry in the United States. Every 4 years, a mail questionnaire, the Physician's Professional Activities (PPA) is sent to all physicians residing in the United States and to US physicians residing temporarily overseas. Each physician is asked to indicate the number of hours worked per typical week within the following categories: professional activity, specialization, and present employment.

Regarding the specialty classification, each physician is asked to indicate the hours spent in primary, secondary, and tertiary activities. A primary specialty is defined by the AMA "as that discipline in which the largest number of hours are reported by the physician on the PPA questionnaire."⁶ Only primary specialties are considered in the *Physician Characteristics and Distribution in the US* publication.

Using information provided by medical schools, hospitals, medical societies, national boards, state licensing agencies, etc, the masterfile is continually updated to reflect the most recent change in address and specialty or professional activity. For a more detailed description of the AMA Physician Masterfile and its contents see the latest edi-

tion of *Physician Characteristics and Distribution in the US*.

This article considers office-based physicians who indicated that pediatrics was their primary specialty during the years 1976 to 1977, 1983 to 1984, 1985 to 1986, and 1987.

The physician's major professional activity as determined from the PPA was divided into two categories—patient care and non-patient care. Patient care included office-based and hospital-based practices (physicians in residency training and full-time members of hospital staffs). Non-patient care activities included administration, medical teaching, research, and other activities. Retired physicians, semiretired physicians, and physicians who indicated that they were inactive for any reason were classified as inactive. This article considered only those physicians who indicated that they had an office-based practice. Included in the office-based practice category were physicians in health maintenance organizations (HMOs), individual practice associations (IPAs), and preferred provider organizations (PPOs).

As defined by the AMA, the field of pediatrics included the following designated subspecialties: adolescent medicine, neonatal-perinatal medicine, pediatric endocrinology, pediatric hematology-oncology, and pediatric nephrology. Pediatric allergy and pediatric cardiology are considered by the AMA to represent separate and distinct medical specialties; these were not considered subspecialties of pediatrics. Thus, physicians who indicated that their primary specialty was either pediatric allergy or pediatric cardiology were excluded from this report. However, in the initial stages of our analyses, we considered the small sample of pediatric allergists and pediatric cardiologists (approximately 380 each). Data based on these groups did not add any new information to the findings concerning the field of pediatrics as defined by the AMA. Pediatricians residing overseas in a US possession also were not considered in this report.

Pediatrician Patient Visits

Each quarter, the Pharmaceutical Database Division of IMS (International Marketing Services) America Ltd publishes the *National Disease and Therapeutic Index*

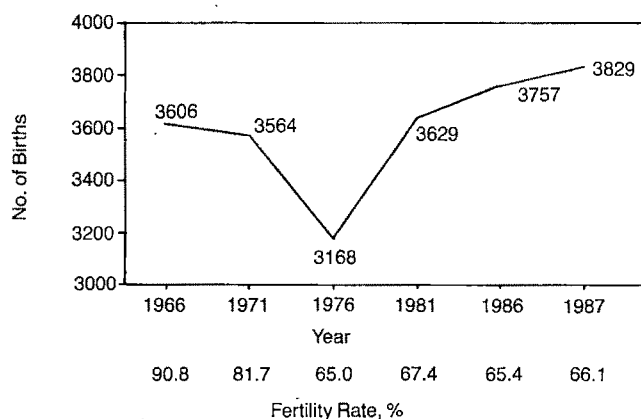


Fig 1.—National births (in thousands) from 1966 to 1987. Note that during the last 20 years the fertility rate of women of childbearing age has decreased from 90.8 per 1000 in 1966 to 66.1 per 1000 in 1987.

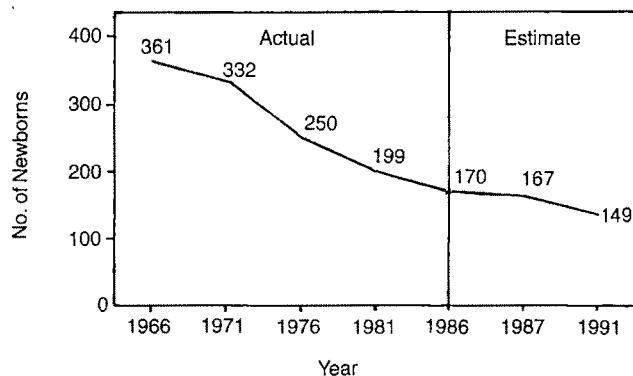


Fig 2.—Number of newborns per office-based pediatrician since 1966 and projected to 1991.

(NDTI).⁶ Based on an audit of office-based physicians, estimates of total patient visits, diagnoses, and drug use are produced. These data are proprietary, and businesses may purchase the NDTI from IMS America Ltd.

Quarterly, a stratified random sample of physicians is initially approached by letter concerning the nature of patient visits from IMS America Ltd. The letter is followed up by a telephone call. Physicians are asked to report on each patient seen or contacted in any way during a 48-hour reporting period. Report forms with instructions are then sent by mail to the physician. The physician is asked to report characteristics of each patient seen, the diagnosis or reason for the visit, and the drug therapy issued. To maintain confidentiality, the names of patients are not reported.

Each quarter, data obtained from more than 2000 physicians are reported. Approximately half the sample is replaced by different physicians each quarter. All office-based physicians are represented within the NDTI sample. The source of physician names is the AMA Physician Masterfile. Of the 2000 physicians surveyed each quarter, more than 140 are pediatricians. For 1987, the sampled pediatricians represented the total population of 22 945 (estimate provided by AMA) office-based pediatricians who reported approximately 132 million patient visits. However, because the sample of pediatricians surveyed was small, to help reduce potential sampling error, this article considers the estimated total number of pediatrician patient visits averaged during 2-year intervals: 1976 to 1977, 1983 to 1984, and 1985 to 1986. We also considered the most current data available, information collected in 1987. A more detailed description of survey methodology and the precision of the estimates can be found in the latest *National Disease and Therapeutic Index*.

Office-Based Pediatrician Potential Market Size

The US Bureau of the Census publishes monthly and yearly estimates of the population of the United States.⁷ The estimates are based on data derived from a variety of sources (see *Current Population Reports*⁷ for a complete discussion of the procedures used in deriving these estimates).

The potential market for pediatric care was calculated by considering the US population of children aged 0 to 2, 3 to 9, and 10 to 19 years average during the 2-year intervals of 1976 to 1977, 1983 to 1984, 1985 to 1986, and during 1987. We used 19 years of age as a cut-off point to assess the US population of children.

The pediatric market share was computed by dividing the number of office-based pediatricians' patient visits by the total number of patient visits (children seeking primary medical care from physicians in any specialty).

RESULTS Demography of the Pediatrician Population

Over the past decade, the population of office-based pediatricians has increased almost twofold from 13 340 in 1976 to 1977 to 22 945 in 1987 (Table). During 1976 to 1981, the compound growth rate was 8%. During 1982 to 1987, this rate was 4%, and the annual growth in 1987 was 4%. If the rate of growth of office-based pediatricians continues at 4% annually, by 1991, we estimate that there will be about 26 800 office-based pediatricians.

During 1981 to 1986, the highest rate of growth of office-based pediatricians (5.0%) occurred in the American Acade-

my of Pediatrics (AAP) district IV⁸ (Florida, Georgia, Kentucky, North Carolina, Puerto Rico, South Carolina, Tennessee, and Virginia). The lowest rate of growth (3.0%) occurred in AAP district V (Indiana, Michigan, and Ohio; pediatricians residing in Ontario, Canada, were not considered).

Pediatric Market: Changing Patient Demography

Recent changes in the demographics of the child population for which pediatricians provide primary medical care have been substantial. These changes correspond to or "echo" those of the postwar baby boom (Fig 1).⁹

The number of births has gradually increased since 1976 and is expected to continue to increase at about 1% annually. Concurrently, there has been a recent, slight decrease in the fertility rate of women of childbearing age (15 to 44 years old; 67 per 1000 in 1981 to 66 per 1000 in 1987). Despite the decrease in the fertility rate, births continue to increase because there are now more women of childbearing age. Echoing the baby boom, the population of young children (<5 years old) will expand reaching its peak in 1990; meanwhile there will be an absolute decline in the adolescent population of 15- to 19-year-olds. The population of adolescents began to fall during the 1970s, shortly after the birth rate reached its peak during the postwar period. The adolescent population will crest in 2005 resulting from the population peak of young children in 1990. Consequently, pediatricians may

Office-Based Pediatrician Market Share Parameters						
Variable	1976-1977*	1983-1984*	1985-1986*	1987	Compound Growth Rate (%) 1976-1977/1987	% Change 1985-1986/1987
No. of pediatricians	13 340	20 104	22 084	22 945†	5.3	3.9
No. of children (in thousands) by age group, y						
0-2	9277	10 717	10 828	11 025	1.7	1.8
3-9	23 912	23 947	24 332	24 892	0.4	2.3
10-19	41 139	36 034	35 412	34 942	-1.5	-1.3
Total	74 328	70 698	70 572	70 859	-0.5	0.4
No. of pediatricians' patient visits (in thousands) by age group, y						
0-2	43 172	57 818	61 046	65 410	4.0	7.1
3-9	33 150	39 092	41 475	43 617	2.7	5.2
10-19	16 647	21 142	20 613	23 460	3.3	13.8
Total	92 969	118 052	123 134	132 487	3.4	7.6
No. of patient visits by age group (y) per pediatrician						
0-2	3236	2876	2764	2851	-1.2	3.1
3-9	2485	1944	1878	1901	-2.5	1.2
10-19	1248	1052	933	1022	-1.9	9.5
Total	6969	5872	5575	5774	-1.8	3.6
No. of pediatric visits per 100 children by age group, y						
0-2	465	539	564	593	2.3	5.1
3-9	139	163	170	175	2.2	2.9
10-19	40	59	58	67	5.0	15.5
Total	125	167	174	187	3.9	7.5
Pediatrician market share (%)‡ by patient age group, y						
0-2	65.0	67.5	68.6	71.8	1.0	4.7
3-9	47.4	52.4	52.8	55.4	1.5	4.9
10-19	15.6	21.3	20.9	24.4	4.4	16.7
Total	38.3	45.5	46.3	49.8	2.5	7.6

*Average during a 2-year period.

†Provided by the American Medical Association.

‡Pediatric market share equals the number of office-based pediatrician patient visits divided by the total number of all patient visits (children seeking primary medical care from physicians in any specialty; not shown in this table).

"recognize a 'wave' in the age distribution of their patients."¹¹

During the last 5 years (1982 to 1987), the highest compound growth rate in the number of US births (50 states) occurred in AAP districts IX (California) (2.6%) and I (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont; Canadian births were not considered) (2.4%). The lowest compound growth rate in the number of births occurred in AAP districts VI (Illinois, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, South Dakota, and Wisconsin) (-1.2%) and VII (Alabama, Arkansas, Louisiana,

Mississippi, Oklahoma, and Texas) (-1.2%).

The number of newborns per office-based pediatrician has substantially decreased from 361 in 1966 to 167 in 1987. If the rate of growth of office-based pediatricians continues at 4% annually and the number of births increases at 1%, the number of newborns per pediatrician will drop to 149 by 1991 (Fig 2).

Although the total number of pediatrician patient visits among children younger than 20 years has substantially increased, from approximately 93 million during 1976 through 1977 to more than 132 million in 1987, the increase in

the number of pediatricians resulted in a decline in the number of patient visits per office-based pediatrician (from 6969 in 1976 through 1977 to 5774 in 1987) (Table). Additionally, noticeable differences are apparent in the number of patient visits per office-based pediatricians according to the age of the patient (Table). Not surprisingly, more children younger than 2 years were seen by a pediatrician as compared with children in older age groups. In 1987, children younger than 2 years were seen at a rate of 593 visits per 100 children. For children aged 3 to 9 years, the rate was 175 visits per 100 children, and for chil-

dren aged 10 to 19 years, the rate was only 67 visits per 100 children.

Pediatric Market Share

The pediatricians' market share of children through 19 years of age (Table) has steadily increased. The office-based pediatricians' market share of children younger than 2 years has increased from 65% in 1976 through 1977 to 72% in 1987. In 1987, children younger than 2 years represented almost half of all pediatrician patient visits. For children aged 3 to 9 years, the pediatricians' market share increased from 47% in 1976 through 1977 to 55% in 1987. The 3- to 9-year-old group comprises about one third of all pediatrician patient visits. The pediatricians' share of the adolescent patient market (ages 10 to 19 years) is relatively small: 16% in 1976 through 1977 and 24% in 1987. This age group represents only 18% of the pediatrician case load.

Potential Marketing Strategies

In discussing potential marketing strategies for the office-based pediatrician, we have selected several key factors that may affect the future role of the pediatrician in providing care to the traditional market population (infants and young children) and to a growing new market (adolescents). The future office-based pediatrician may face losses of patient visits primarily because more physicians will be competing for the same patient population. However, local economic factors and changing birth rates may also have an influence on the future pediatric practice. As a result, pediatricians may be forced to select a number of marketing strategies to maintain and increase their share of the patient population. Key marketing principals that may foster the growth of the pediatric practice have been considered by others,^{3,10-15} and some are briefly outlined below.

Location.—Knowing about the current population base near an office provides great insight into how to target services. For example, an expected population increase of children younger than 4 years in a specific geographic area in the next 5 years may provide support for adding a satellite facility. Additionally, as mentioned earlier, in the last 5 years, the greatest increase in

the number of US births has occurred in AAP districts IX and I. Demographic profiles in selected areas in these districts or in other areas of population growth may provide important information when considering relocating or starting a pediatric practice. Brown and Morley¹⁰ provide a list of places where such demographic information may be obtained.

Patient Satisfaction.—Data collected from an existing patient base may lead to a better understanding of how well patients feel about the services being offered. Courteous and timely treatment by staff, personal and warm relationship with the physician, quality medical information, use of educational materials considered valuable by patients, and comfortable physical surroundings are keystones for meeting patient's needs. A patient questionnaire that addresses these issues is probably one of the most important marketing tools.¹⁰ The information provided by a patient survey may not only measure patient satisfaction but also may define accurately a service area (How far will people drive to visit an office?).

Convenient Hours and Accessibility.—The single-parent family and families in which both parents work now predominate. The 9-to-5 office hours offered by many physicians may not conform to the schedule of the average patient. Evening and weekends office hours, and telephone accessibility, may attract patients who are concerned with convenient and professional services. Physicians who are more accessible to patients by making house calls, offering telephone consultation, and opening more offices may offer additional convenience to the existing or new patient.

New Patient Markets.—Increasing numbers of adolescents are seeking care from pediatricians. As Kappy⁴ has suggested "adjusting office hours to avoid mixing infants and adolescents, acquiring new skills to care for adolescents (eg, sports participation examinations, pelvic examinations, counseling, prescription of unfamiliar medications), addressing unique ethical issues, and facing economic problems in funding such care" represent new challenges and opportunities for the future pediatrician.

Becoming more involved in community activities may provide access to new

patients markets. Offering to speak about such topics as nutrition, sports-related injuries, drunk driving, and seat belt safety would represent a unique and effective approach to make personal and professional contact with civic and business organizations, Parent-Teacher Associations, and high schools.

In addition to the marketing techniques described above, several investigators¹⁰⁻¹⁶ have outlined other innovative techniques and strategies for developing and implementing an effective physician marketing plan.

COMMENT

Data presented herein provide an overview of the demography of office-based pediatricians, recent trends in patient population, and the present status of the pediatric market share. This study amplifies and updates previous investigations of the characteristics and future opportunities of practicing pediatricians.¹⁻⁴ It differs from other investigations because it centers on the current status of the pediatricians' market share of infants and children as determined from the latest nationally representative data. From this standpoint, only the report by Nadler and Evans² is comparable. However, Nadler and Evans describe market share data from 1964 to 1984 using information provided by Martinez⁹; details of methodology and a description of more recent data as described in the present report have not been published elsewhere.

The results presented herein show that four factors bear directly on the present and future status of the office-based pediatric practice: (1) the size of the office-based pediatrician population, (2) the size of the pediatric patient population, (3) the frequency of patient visits per office-based pediatrician, and (4) the size of the market share of the patient population. It seems that the rate of growth of the pediatrician population has outpaced increases in the birth rate of young children. As a result, the number of potential patients per pediatrician has undergone a net decline. Despite these changes in the pediatrician and patient populations, it is encouraging that the pediatricians' market share of young children has continued to grow. To date, pediatricians have realized more than 70% of the

market share of patients younger than 2 years.

It seems evident that the opportunity to expand the pediatricians' market share of young children may be limited. The pediatricians' share of young children may not grow fast enough to offset the increase in the population of pediatricians.

Growth of the pediatric practice may depend on providing more primary medical care to the adolescent population. The pediatricians' market share of children aged 10 to 19 years is growing and in 1987 the market share was 24%; the potential for continued growth exists. By defining the age limits of pediatrics, the Council on Child and Adolescent Health¹⁶ makes a strong case for changing the pediatricians' traditional focus on children under 10 years of age. The Council states that "the responsibility of pediatrics may begin with the fetus and continue through 21 years of age."¹⁶

Future growth of pediatrics may depend on the rate of growth of the pediatrician population. The Committee on

Pediatric Manpower¹⁷ offers several recommendations that are consistent with improving the quality of care available to children. Development of effective marketing strategies also may help increase the pediatricians' share of the patient population.

It is hoped that the information provided herein will be useful to health planners to ensure the continued growth of pediatrics and its high quality of care for children.

Linda Goode helped prepare the manuscript. Gene Roback provided the AMA estimate for the number of office-based pediatricians.

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Shmuel Davidson, MD; Doras Creter, MD; George Leventon, MD; Daniel Katznelson, MD (*Arch Otolaryngol Head Neck Surg*. 1989;115:876-877)

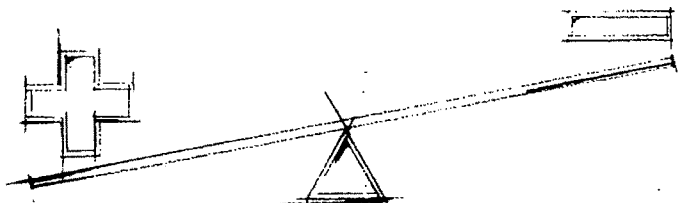
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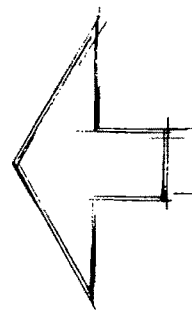


The *Compendium of Patient Safety and Medical Risk Management Programs* is a comprehensive listing of patient safety/risk management resources available from the AMA/Specialty Society Medical Liability Project, the American Medical Association, the Council of Medical Specialty Societies, the Physician Insurers Association of America, national medical specialty organizations and state medical associations.

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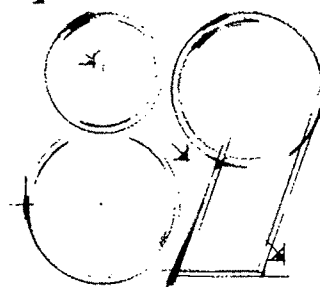
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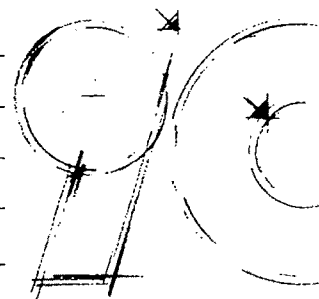
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Educational Interventions



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Purpose.—This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.

Editorial Comment.—*What kind of training do pediatric residents receive regarding head injuries? This study reports a survey of pediatric residency programs regarding whether such training took place, and also the type of training that was used. Apparently, we train adequately regarding acute management, but education about the long-term effects of head injuries is seldom provided. This important aspect is discussed herein.*—H.D.A.

Head Injury Training for Pediatric Residents

Janet S. Tyler, PhD; Mary P. Mira, PhD; Joseph G. Hollowell, MD, MPH

Annually, approximately 100 000 children under the age of 15 years suffer traumatic head injury severe enough to be hospitalized.¹ Advances in medical technology and trauma care are enabling more children to survive previously fatal head injuries. Therefore, pediatricians will be called on increasingly to treat and give advice regarding children who have survived traumatic head injuries.

Recently, professionals who treat children with head injuries have recommended that pediatricians become involved in the long-term follow-up of children with head injuries,² even when the injuries are only mild to moderate.³ This is an important recommendation because the majority of head injuries are classified as mild.⁴

This request for the careful monitoring of children with head injuries stems from recent evidence that even mild injuries may result in long-term physical sequelae, such as seizures⁵ and motor

impairments,⁶ as well as psychosocial and cognitive consequences.⁷ Research has indicated that approximately 25% to 30% of children with head injuries may require some form of special educational services.⁸

Because a pediatrician is believed to be the specialist who is best prepared to interpret medical data for school personnel,⁹ pediatricians will increasingly be called on to participate in interdisciplinary efforts,¹⁰ to collaborate with school personnel to serve children with disabilities,¹¹ and to give advice on the long-term rehabilitation of children with head injuries. Therefore, it is important to know what is available for training pediatricians in the area of head injuries. This article will report the results of a survey of pediatric residency training programs conducted to obtain information on the scope and depth of training in head injuries.

MATERIALS AND METHODS

In February 1988, a seven-page questionnaire booklet was mailed to the 227 directors of pediatric residency training programs in the continental United States. The names of the program directors and the addresses of the programs were obtained from the 1987 to 1988 edition of the *Directory of Residency Training Programs*.¹²

Ten days after the questionnaires were mailed, reminder postcards were mailed to all nonrespondents. In an effort to increase response rate, approximately 6 weeks after the initial mailing, duplicate questionnaires were sent to all nonrespondents.

The questionnaire asked about size and type of hospital and pediatric service. Pediatric training directors were asked to indicate from a list of topics relating to head injury which topics were covered during residency. They were also asked to indicate the format(s) for traumatic head injury training from the following format choices: (1) regularly scheduled conference or lecture, (2) problem case conference, (3) required readings, (4) random clinical exposure, or (5) planned clinical exposure.

Other survey questions included whether residents had rotations in the intensive care unit or neurology department, whether there was a formal evaluation of residents' knowledge of traumatic head injury, and who was responsible for providing pediatric rehabilitation care and follow-up.⁷

RESULTS

Responses were received from 110 (48%) of the 227 programs surveyed. Responders and the original sample were compared using directory data on the annual number of inpatient admissions. In the original sample 33% of the hospitals were considered small (<3000 inpatient admissions), 40% of the hospi-

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From the Children's Rehabilitation Unit, University of Kansas Medical Center, Kansas City.
Reprint requests to Children's Rehabilitation Unit, University of Kansas Medical Center, 39th & Rainbow Blvd, Kansas City, KS 66160 (Dr Tyler).

Table 1.—Designated Responsibility for Rehabilitation Care	
Department	No. (%) of Responses of Pediatric Directors
Rehabilitation medicine	46 (41.8)
General pediatrics	22 (20.0)
Combination of services	17 (15.5)
Other medical specialties	6 (5.5)
Neurology	5 (4.5)
Referred elsewhere	5 (4.5)
Neurosurgery	4 (3.6)
No one responsible	4 (3.6)
No response	1 (1.0)
Total	110 (100.0)

Table 2.—Number of Programs Covering Each Topic Relating to Pediatric Head Injury	
Topic	No. (%) of Programs
Emergency department trauma	98 (89)
Neurosurgery	81 (74)
Prevention	73 (66)
Acute rehabilitation	52 (47)
Head injury effects vs developmental delays	52 (47)
Long-term rehabilitation	47 (43)
Cognitive/language	43 (39)
Psychosocial sequelae	40 (36)
Cognitive retraining	39 (35)
Counseling families	37 (34)
School/community reentry	31 (28)
No planned topic	7 (6)

tals were considered medium (3001 to 7000 inpatient admissions), and 27% were considered large (7001 to >10 000 inpatient admissions). Of those responding, 29% were from small hospitals, 42% were from medium-sized hospitals, and 29% were from large hospitals. Therefore, based on hospital size, the distribution of those responding was representative of the original sample. Thirty-three (30%) of the programs responding were located in a children's hospital.

Almost all of the programs (97%) responded that pediatric house officers rotate through an intensive care unit. For 98% of those respondents, the rotation was required. In 96% of the programs, pediatric house officers rotate through the neurology department (in 51% of the programs this was a required rotation). Long-term follow-up of pediatric patients with head injuries was a responsibility of the neurology service in 74% of the programs.

A formal evaluation of pediatric residents' knowledge of traumatic head injury occurred in 17% of the programs. The type of evaluation varied among hospitals (eg, written examination, clinical competence in head injury care and rehabilitation, or a combination of evaluation forms).

The responses of pediatric directors asked "In your hospital who is responsible for providing pediatric rehabilitation care?" are shown in Table 1. Rehabilitation medicine (42%) was the most frequently designated profession responsible for pediatric rehabilitation care. In 20%, general pediatrics was responsible for rehabilitation care, while a combination of services rather than one department was noted by 16% of the respondents. The remaining 22% of the respondents were divided among the following: medical specialties (eg, orthopedics, child development, trauma team), 5.5%; neurology, 4.6%; referred elsewhere, 4.6%; neurosurgery, 3.7%;

and no designated responsibility, 3.7%.

Head Injury Training

Table 2 shows the distribution of topic areas among programs providing planned exposure to each of the topics. The format random clinical exposure was not included in this tabulation.

Training topics reported by more than 50% of programs included emergency department trauma care of head injuries (89%), neurosurgical stabilization of head injuries (74%), and prevention of head injuries (66%). The topic covered by the fewest number of programs was the reentry of the child with a head injury to the school and community (28%).

The number of head injury topics covered varied greatly from no training in any topics listed to training in all of them. As an index of a program's overall intensity of head injury training, the total number of head injury topics covered was determined. For each program that offered planned training the number of different topics was summed and the most frequent number of head injury topics reported was three (19% of the programs covered three topics). It is interesting to note that in all cases where only one or two topics were covered, the topics dealt exclusively with prevention or some aspect of acute care. For those programs covering three topics (21 programs), 52 of the 63 topics also dealt with prevention or acute care of head injuries.

There was no apparent correlation between the size of the hospital program (annual number of inpatient admissions) and the extent of planned training offered pediatric residents, based on the number of topics covered. Furthermore, the analysis of the data did not point to any pattern of relationship between comprehensiveness of the training (ie, number of topics covered) and the service responsible for caring for these children.

COMMENT

The results of this survey indicated that scope and depth of training in head injury varied greatly among pediatric residency programs. It was shown that over 60% of the programs provided training in head injury prevention and acute care. However, approximately

half of the programs do not offer any planned training in head injury beyond the acute-care phase. Education regarding the long-term effects of traumatic head injuries or their management is extremely limited. Furthermore, only a limited number of programs formally evaluate their residents' knowledge of traumatic head injury.

Although training in the acute-care phase of head injuries is vital, that phase is a relatively short part of the injured child's life. The pediatrician often does not resume care of the child with a head injury until after the acute-care phase. Therefore, the pediatrician needs to be knowledgeable about the long-term effects of head injury so services can be provided and advice can be offered to parents and school personnel. Currently many pediatricians are not receiving any training in this area.

Our results indicate a lack of a systematic approach to the education of pediatric residents regarding head injuries. Ideally, such training should cover the full spectrum of issues faced by the injured child and family. Not only should issues beyond acute care be addressed through systematic training means (ie, planned clinical exposure, case conferences, etc), but also this broad spectrum of issues should be woven into the vehicles for care available in the existing training programs. For example, a site could be via the continuity clinics in which the resident provides primary care for the child with a head injury who is also being seen in other specialty clinics. Only a few patients would need to be seen for many aspects of rehabilitation to be presented. Building on the continuity process, prevention of head injuries and cognitive, academic, and family issues could be addressed. In the continuity process, when questions about the care of the injured child beyond the acute phase arise, residents have the resources of other professionals and the available

body of literature, thus increasing the breadth of the exposure.

There are also opportunities for this training within existing training formats. The intensive care unit and neurology rotations may be potential training sites for addressing long-term aspects of traumatic head injury. The majority of trainees have these rotations and in the majority of programs (74%) the neurology service offered long-term follow-up of pediatric head injuries.

Given the results of this survey, provision of services provided to children who have sustained traumatic head injuries may need to be reconsidered. Our data indicated that the medical specialty responsible for rehabilitation care varied among hospitals (with some programs reporting no one was responsible). In other words, there currently exists no standardized procedure for monitoring the long-term rehabilitation care of the child with a head injury.

Another important issue is that the acute-care specialist needs to be aware that the problems of head injury are not short-term, and to alert rehabilitation specialists early on so that planning for long-term rehabilitation may start during early recovery. Because the child's recovery will be long-term, it is important to establish as a routine the involvement of the full range of rehabilitation specialists early in the child's care. Therefore, early consultation would be considered an important part of head injury care. Ideally, consultations should begin while the child is still being cared for in the intensive care unit.

In summary, some important issues about head injury training need to be considered. First, with medical technology improving, more children will survive traumatic head injuries and return to school. Second, it has been established that traumatic head injury may cause long-term physical, cognitive, and behavioral sequelae. Third, parents

and school personnel are relying on pediatricians to guide them through the long-term recovery of the child's head injury. Therefore, pediatricians need to receive training in head injury beyond the acute-care stage. Pediatricians need to be knowledgeable about the long-term sequelae of head injury and to be aware that these children will need long-term rehabilitation and follow-up. While other studies are needed to define the knowledge base of residents in head injury, this study has shown that many residents are not receiving training in this important area.

This study was supported in part by Title VI-B grant 8805-FY88 from the Kansas State Department of Education, Topeka, Kan, and federal government grants MCJ-000944 from the Department of Health and Human Services, Rockville, Md, and ADD-07DD0262-17 from the Administration on Developmental Disabilities, Department of Health and Human Services, Washington, DC.

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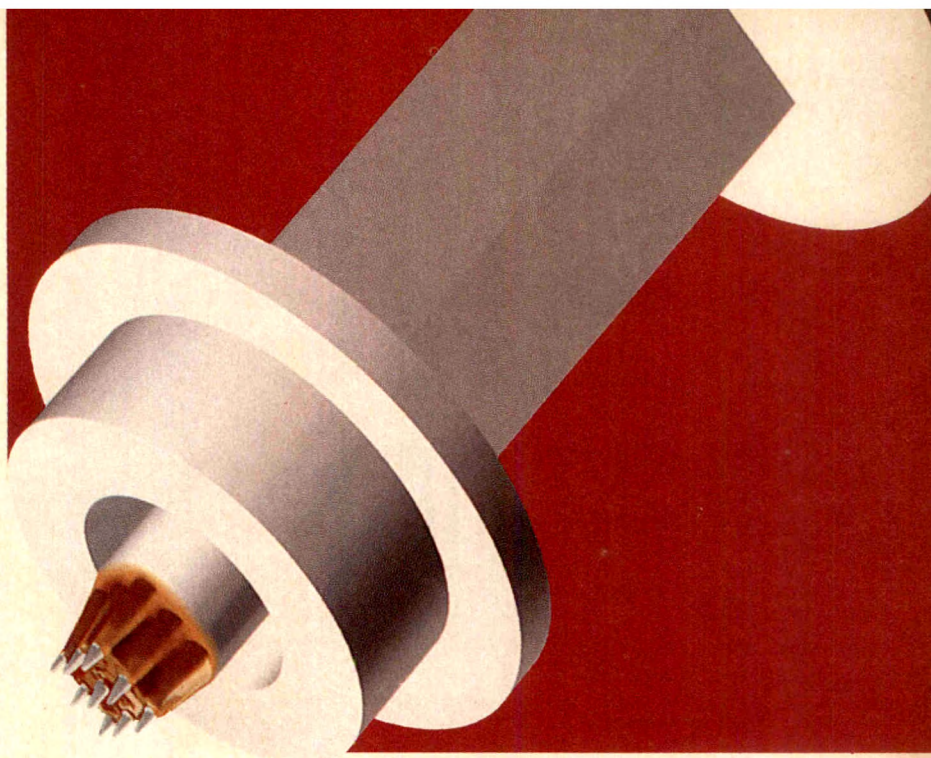
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Book Review

Textbook of Pediatric Emergency Medicine, 2nd ed, edited by G. Fleisher and S. Ludwig, 1388 pp, \$112.50, Baltimore, Md, Williams & Wilkins, 1988.

Fleisher and Ludwig have taken on an Olympian task. In the *Textbook of Pediatric Emergency Medicine*, the editors have attempted to provide a single informative source of the pathophysiology, differential diagnosis, and acute management of practically all pediatric conditions that the emergency department practitioner will encounter. They have done a superb job.

The book is divided into six sections. The first is devoted to life-support emergencies, the hallmark of emergency department practice. The second section, titled "Signs and Symptoms," includes the pathophysiology, differential diagnosis, and essential aspects of clinical evaluation for specific complaints that bring children to the emergency department. The third, fourth, and fifth sections, titled "Medical Emergencies," "Surgical Emergencies," and "Psychosocial and Medicolegal Emergencies," respectively, focus in more detail on most of the conditions identified in section 2. The final section illustrates 55 procedures frequently performed in caring for children in the emergency department. Helpful appendixes provide information on pediatric resuscitation equipment for use in the emergency department, office, or clinic, and a list of pediatric resuscitation drugs.

This book is a second edition. Nearly all chapters have been rewritten with new tables, algorithms, and illustrative roentgenograms. In the "Signs and Symptoms" section, tables of both common and life-threatening causes have been added. There are new, well-written chapters on important topics such as apnea, heart murmurs, the septic-appearing infant, sore throat, visual disturbances, and wheezing. Other new chapters cover neonatal resuscitation, the approach to trauma, metabolic emergencies, bites and stings, radiation injuries, and pulmonary emergencies. The chapter on jaundice has been enhanced by being divided into two chapters on conjugated and unconjugated hyperbilirubinemia.

Because of the rapid growth of medical knowledge, many textbooks are out of date by the time they are published. Fortunately, this book has largely avoided that pitfall: the newer cephalosporins, with dosing recommendations, have been included, and pulse oximetry is mentioned as a monitoring aid. The resuscitation section includes a good discussion on the limits of bicarbonate therapy, the use of "quick-look" paddles for determination of cardiac rhythm, and the intracosseous infusion technique. New management algorithms for asystole, bradycardia, ventricular fibrillation, and electromechanical dissociation are presented.

One cannot expect a text that explores an immense, rapidly growing field to be perfect, and there are a few problems worth noting. Although the book covers most of the clinical conditions encountered, it omits a thorough discussion of the management of children with human immunodeficiency virus infection. The emergency department is the most likely place these children present, and

their problems are unusual enough to deserve special mention. On the one hand, certain presenting complaints may suggest the possibility of human immunodeficiency virus infection long before "classic" or textbook conditions associated with the acquired immunodeficiency syndrome have manifested themselves. Alternatively, the child with human immunodeficiency virus infection who has a common complaint (such as fever) may require a different evaluation and disposition from that of the healthy child with a similar complaint.

Other problems occur in the area of management recommendations. Epinephrine, susphrine, and theophylline are described as the mainstays of asthma therapy. In many emergency departments, the use of β -agonists has made susphrine obsolete. Use of metered-dose inhalers is gaining popularity as first-line therapy for discharged asthmatics, particularly with the development of newly designed adjunctive devices that facilitate their use by younger children. Susphrine and theophylline are also recommended for infants with bronchiolitis who respond to epinephrine therapy. We have noted several cases of theophylline toxicity in young infants treated with theophylline for bronchiolitis; thus, we almost never use it on an outpatient basis in infants less than 6 months of age.

Consideration of chlamydial infection in children being evaluated for either sexual abuse or gonorrheal infection is not discussed, although concern for this clinical problem is increasing in many emergency departments.

Finally, a detailed management algorithm for children with suspected epiglottitis would have been helpful, serving as a model for institutions that do not already have a protocol in place for dealing with this fulminant infection. Directing the practitioner to place an intravenous line in the "cooperative" patient with epiglottitis suggests that it is an acceptable practice to restrain the child or insist that she or he lie down. Moreover, the insistence on a lateral neck roentgenogram could cause unnecessary delay in securing an adequate airway. I don't consider it desirable to obtain the lateral neck roentgenogram in the child with probable epiglottitis (although many physicians will obtain one). Instead, I consider it to be most helpful in those situations where the primary diagnosis is croup but the possibility of epiglottitis hasn't been ruled out.

To focus on this book's few problems, however, is really unfair. It's a bit like criticizing an Olympic gold medalist for not simultaneously breaking the world record. In this new edition of *Textbook of Pediatric Emergency Medicine*, Fleisher and Ludwig have tackled an Olympian task and have come through with flying colors. Their book is a major achievement for which emergency department practitioners will be extremely grateful.

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Clinical and Bacteriologic Features of Chronic Sinusitis in Children

David G. Tinkelman, MD, Howard J. Silk, MD

• The clinical and bacteriologic aspects of chronic sinusitis in childhood were studied. Of 35 children who underwent surgical procedures for chronic sinusitis, 22 had positive bacteriologic cultures of aspirates from the sinus. The most common organisms isolated were *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Branhamella catarrhalis*. Five of eight *S pneumoniae* strains were relatively resistant to penicillin and resistant to sulfamethoxazole-trimethoprim. All of the *B catarrhalis* and 20% of the *H influenzae* organisms were β -lactamase positive. Overall, 14 of 28 of the bacteria were penicillin resistant. In addition, all 12 children 2 years of age or younger had a positive bacterial culture as compared with much lower rates in older children. Although the incidence of *S pneumoniae* strains that are relatively resistant seems to be rising, to our knowledge we report the first description of these organisms as significant pathogens in chronic childhood sinusitis. These results indicate that chronic, difficult to manage sinusitis in very young children is frequently bacterial in origin, especially if the patient is 2 years old or younger. In light of the frequent failure of antibiotic therapy and considering the incidence of relatively resistant *S pneumoniae* strains, puncture of the sinus should be considered early in the course of chronic sinusitis to isolate pathogenic organisms and determine appropriate antimicrobial therapy.

(AJDC. 1989;143:938-941)

During the past several years, sinusitis has been increasingly recognized in childhood. The studies of Wald

For editorial comment see p 886.

et al¹⁻³ have shed new light on the clinical and bacteriologic aspects of this disease.

Accepted for publication February 27, 1989.

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Unlike the predominant organisms in acute sinusitis, which include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Branhamella catarrhalis*,¹ chronic sinusitis may yield anaerobic isolates.⁴ Despite multiple courses of antibiotics, chronic sinusitis is often unremitting, and patients frequently require referral to an otolaryngologist for surgical management. We undertook this study to evaluate the clinical and bacteriologic findings of chronic sinusitis in a group of children who underwent surgical procedures for this condition.

PATIENTS AND METHODS

The records of 116 consecutive children who underwent surgical procedures for chronic sinusitis at four metropolitan Atlanta, Ga, hospitals during a 12-month period were reviewed. Charts were considered to be complete if they contained all of the following: complete medical records, including sinus roentgenograms, aerobic and anaerobic cultures of sinus aspirates, antibiotic sensitivities, and complete records of antimicrobial therapy. Of the 116 patients, 77 were excluded from evaluation as culture and sensitivity results were not obtained, and 4 were excluded due to lack of sinus roentgenograms. Therefore, 35 patients were considered eligible for evaluation.

Clinical signs and symptoms of chronic sinusitis included purulent nasal discharge, cough (often nocturnal), facial pain or swelling, sore throat, or headache that were present for greater than 30 days.

Sinus roentgenograms (anteroposterior, occipitontental, and lateral views) were obtained in all patients and were reviewed by a radiologist at the time of presentation. The roentgenograms were interpreted either as normal or abnormal based on evidence of opacification, air-fluid levels, or a mucosal thickening of 5 mm or greater.¹

If there was no clinical improvement after therapy with antimicrobial agents and antihistamines or decongestants, patients were considered treatment failures and were con-

sidered candidates for surgical intervention. Treatment courses with antibiotics ranged from 10 to 21 days each.

Surgery was performed at one of four metropolitan Atlanta hospitals. All patients underwent irrigation and drainage of the maxillary sinuses; nasoastral windows were placed and adenoidectomy was performed as deemed appropriate by the individual otolaryngologist.

Sinus aspirates were obtained after swabbing of the nasal mucosa with povidone-iodine solution, which was allowed to dry. The nasal wall was punctured in the area of the inferior turbinate, and the sinus was aspirated. If no secretions were obtained, the sinus was irrigated with 1 to 3 mL of nonbacteriostatic saline and reaspirated. Air was evacuated from the syringe. The needle was removed, and the syringe was capped and transported to the microbiology laboratory where samples were plated within 30 minutes of collection.

Sinus aspirates were plated onto chocolate agar for aerobic culture and were plated onto prereduced anaerobic blood agar with kanamycin sulfate and vancomycin hydrochloride for anaerobic growth. Three anaerobic plates were incubated in anaerobic jars and examined at 48 and 96 hours. Bacterial isolates were identified by standard methods⁵ and were considered significant if at least 10⁴ colony-forming units per milliliter were recovered.¹ Isolates were screened for penicillin sensitivity by the disk diffusion method using 1- μ g oxacillin sodium disks on commercial agar (Mueller-Hinton) plus 5% sheep's blood.⁶ Strains that showed an inhibition zone of 20 mm or less on the 1- μ g oxacillin disk were considered relatively resistant to penicillin.^{6,7} Strains of *H influenzae* and *B catarrhalis* that were resistant to ampicillin were tested for β -lactamase production.⁸ Antibiotic sensitivities were otherwise determined by the Kirby-Bauer method.⁹

RESULTS

The medical records of 35 children were eligible for entry into the study. Males outnumbered females 26 to 9. The children ranged in age from 10 months to 16 years (mean \pm SD, 4.9 \pm 3.9 years).

Symptoms and Treatment

The preponderant symptoms in these patients were purulent rhinorrhea, postnasal drip, or both occurring in 27. Fourteen patients had a cough, often nocturnal, another 3 children had episodes of wheezing, and 10 children had both drainage and coughing. All 35 children had roentgenographic evidence of sinusitis, 32 of 35 had complete opacification of at least one maxillary sinus, and the remaining 3 children had substantial mucosal thickening of 5 mm or greater. Four patients had pansinusitis. Isolated frontal sinus disease was not found. Eleven patients had a history and physical examination results compatible with allergic rhinitis. The IgE levels and immunoglobulin values were not available for all patients.

All children were receiving antimicrobials at the time of their surgical procedures. Thirty children had at least two previous courses of different antibi-

otics, 14 had three courses, 7 had four different antibiotics, and 1 child received five different antibiotics. The most commonly used antibiotics, listed in order of decreasing frequency, were as follows: cefaclor, amoxicillin, sulfamethoxazole-trimethoprim, amoxicillin-clavulanate, potassium, erythromycin ethylsuccinate, cephalexin, and doxycycline hyclate. The number of antibiotic courses before obtaining cultures did not correlate with bacteriologic recovery. Each antibiotic was used for 10 to 21 days at a time.

All patients had irrigation and drainage of their maxillary sinuses, 29 children also underwent placement of antral windows, and 10 patients underwent adenoidectomy as well. There were no surgical complications. Twenty-two of 35 families reported clinical improvement following the procedure, and 13 reported no change.

Bacteriologic Findings

In this cohort, 28 bacterial isolates were recovered from 22 of 35 patients (Table 1). Nontypeable *H influenzae* and *S pneumoniae* were cultured most frequently (8 patients each), followed by *B catarrhalis* (4 patients), *S aureus* (3 patients), group A *Streptococcus* (3 patients), *Staphylococcus warneri* (1 patient), and *Streptococcus sanguis* (1 patient). Two different organisms were recovered from 4 children, and 1 child had 3 bacterial species recovered. Two of the 8 *H influenzae* isolates and all 4 *B catarrhalis* isolates were β -lactamase positive. No anaerobic organisms were recovered. Five of the 8 strains of *S pneumoniae* isolated were relatively resistant to penicillin, with less than 12 mm of diffusion on 1- μ g oxacillin disks. All 5 were also resistant to sulfamethoxazole-trimethoprim; in 1 patient

the strain was resistant to gentamicin sulfate as well. All were sensitive to second- and third-generation cephalosporins, clindamycin hydrochloride, vancomycin, and chloramphenicol. Sensitivities to amoxicillin-clavulanate were not obtained (Table 2). Three of the patients with *S pneumoniae* strains relatively resistant to penicillin also had β -lactamase-negative *H influenzae* recovered from their sinuses; 1 patient had *B catarrhalis* recovered. All 5 children with relatively resistant *S pneumoniae* strains had received a β -lactam drug before surgery and were younger than 3 years old. Overall, 14 of 28 of the isolates were resistant to the penicillins.

There was a strong positive correlation between age and positive bacterial cultures. All 12 children who were 2 years of age or younger had a positive culture compared with 7 of 12 children between 2 and 5 years of age and one fourth of the patients older than 10 years (Table 3). The number of preoperative antibiotics did not differ between age groups and did not correlate with culture results.

COMMENT

Although acute sinusitis in children has become a well-recognized clinical problem,^{1,4} there remains a scarcity of data concerning chronic childhood sinusitis.

In this group of children with chronic sinusitis, 22 of 35 had bacteria isolated from their paranasal sinuses compared with approximately 75% of children with acute sinusitis as reported in the literature.¹ The bacteriologic characteristics of chronic sinusitis in this patient population are similar to those of acute infection, with *H influenzae*, *S pneumoniae*, and *B catarrhalis* being recovered most frequently. A study by

Table 1.—Number of Bacterial Isolates and Penicillin Sensitivity

Organism	No. of Isolates	No. of Penicillin-Resistant Isolates
<i>Haemophilus influenzae</i>	8	2
<i>Streptococcus pneumoniae</i>	8	5
<i>Branhamella catarrhalis</i>	4	4
<i>Staphylococcus aureus</i>	3	3
Group A <i>Streptococcus</i>	3	0
<i>Staphylococcus warneri</i>	1	0
<i>Streptococcus sanguis</i>	1	0
Total	28	14

Table 2.—Sensitivities of Relatively Resistant Pneumococci*

Patient Age, y	Penicillin	Oxacillin Sodium	Sulfamethoxazole-trimethoprim	Gentamicin Sulfate	Erythromycin Ethylsuccinate	Cefamandol	Cefuroxime	Ceftriaxone Sodium	Chloramphenicol	Vancomycin Hydrochloride
1.5	R	R	R	S	S	S	S	S	S	S
1.8	R	R	R	S	S	S	S	S	S	S
0.8	R	R	R	S	S	S	S	S	S	S
2.8	R	R	R	R	S	S	S	S	S	S
1.3	R	R	R	S	S	S	S	S	S	S

*R indicates resistant; S, sensitive.

Table 3.—Positive Culture Rate by Age

Age, y	No. of Positive Cultures/ Total No. of Patients
0-2	12/12
>2-5	7/12
>5-10	2/7
>10	1/4
Total	22/35

Brook⁴ isolated anaerobic bacteria in 37 of 40 children with chronic sinusitis. The results of our study could not confirm the prevalence of anaerobes as significant pathogens. However, differences in laboratory technique and antibiotic use at the time of surgery may have resulted in the lack of anaerobic recovery. Our patient population was also significantly younger than that of Brook⁴ (mean, 4.9 vs 11 years), whose patients were all older than 6 years. This age differential may also account for the differences seen in the bacteriologic characteristics of chronic sinusitis. Preliminary data from Rachelefsky et al¹⁰ isolated only one anaerobe from eight children with chronic sinusitis. Anaerobic organisms, therefore, may not play as large a role in chronic childhood sinusitis as previously thought.

All 12 children 2 years old or younger had positive sinus cultures as compared with 22 of 35 children overall. This correlation was striking and, to our knowledge, has not been previously reported. Age was the only variable that correlated with a positive culture; clinical symptoms, white blood cell counts, and type and frequency of antibiotic therapy were not associated with a positive result. Predisposing factors for sinusitis in children include obstruction of the sinus ostium secondary to upper respiratory tract infections, allergy, nasal polyps, immotile-cilia syndrome, immunodeficiency syndromes, and foreign bodies. In particular, the role of viral upper respiratory tract infections, allergy, and immune dysfunction may contribute to the high recovery rate of bacteria in those younger than 2 years. Immunoglobulin levels and atopic status were not determined for the majority of our patients, and therefore we cannot draw any conclusions as to whether these factors played a role in the age-associated culture results.

The recovery of relatively resistant *S*

pneumoniae strains from five patients was of great interest. Prevalence rates of these strains may range as high as 3% to 16%^{11,12} in the pediatric population, with nasopharyngeal carriage rates of 14% to 49%¹³ in selected geographic populations. While episodes of pneumonia, meningitis, bacteremia, and otitis media due to relatively resistant *S pneumoniae* strains have been reported,^{14,15} to our knowledge this is the first demonstration of the entity in association with chronic sinusitis in children.

Because of the retrospective nature of this study, the relatively resistant strains of *S pneumoniae* were not available for minimum inhibitory concentrations to be obtained. Although the minimum inhibitory concentration is the definitive method for determining penicillin resistance, all five pneumococcal strains had inhibition zones of 12 mm or less on 1- μ g oxacillin disks, which is considered to be a highly selective screening method for determining resistance to penicillin, although it cannot distinguish between true penicillin resistance and relative penicillin resistance.¹³ We cannot conclusively state that these were truly penicillin-resistant strains of *S pneumoniae*, and, therefore, are considering them to be relatively resistant.

Pneumococci also seem to be increasingly resistant to sulfamethoxazole-trimethoprim,^{13,16} and all five strains relatively resistant to penicillin were resistant to sulfamethoxazole-trimethoprim as well. As previously documented,^{14,15} all of the children in this cohort with strains relatively resistant to penicillin were younger than 3 years and had been treated with a β -lactam drug; four of five patients had also received sulfamethoxazole-trimethoprim. Thus, previous therapy with a β -lactam antibiotic or sulfamethoxazole-trimethoprim presumably selects for the relatively resistant pneumococci, particularly in areas such as the paranasal sinuses, where there is relatively poor penetration of the penicillin antibiotics.^{17,18} Age also seems to be a risk factor for infection with strains relatively resistant to penicillin, possibly caused by the increased rate of pneumococcal infection in young children as well as their relative inability to mount a humoral response to polysaccharide antigens.

Retrospective studies have limitations. The exclusion of 77 of 116 patients from this study was necessary since culture and sensitivities were not obtained on the sinus aspirates. However, the 35 patients studied do not differ in age or clinical symptoms from those excluded. Although the sample size is small, it is similar to that of other studies of childhood sinusitis.¹⁴ Nevertheless, these data must be considered preliminary, with prospective follow-up studies necessary for confirmation.

Because of the differences in antibiotic sensitivities between different strains of relatively resistant *S pneumoniae* and the preliminary nature of our data, one needs to be cautious with therapeutic recommendations. Cefaclor has been shown to be less effective than other cephalosporins for use against these strains,¹⁶ which is supported by our study, in which cefaclor was the most widely prescribed antibiotic, although it did not seem to alter the bacteriologic recovery of relatively resistant strains of *S pneumoniae* or to change the clinical findings. Other cephalosporins such as cefuroxime or ceftriaxone sodium may be more effective in eradicating these infections,¹⁶ and our data support this as well (Table 2). As penicillin resistance in pneumococci is caused by alterations in penicillin-binding proteins¹⁹ rather than β -lactamase activity, treatment with amoxicillin-clavulanate potassium would not seem to be an effective antimicrobial for relatively resistant strains, although sensitivities were not obtained to confirm this theory. Other alternate antibiotics may include erythromycin, chloramphenicol palmitate, and vancomycin.

The standard course of therapy for sinusitis is 10 to 14 days, although some authors now recommend a 21- to 28-day course. The beneficial use of antihistamines and decongestants has also not been sufficiently documented.

In light of the increasing incidence of relatively resistant strains of *S pneumoniae* and the high rate of bacteriologic recovery in young children with chronic sinusitis, these preliminary data indicate that diagnostic sinus puncture should be considered early in the course of chronic sinusitis to isolate pathogenic organisms and to select appropriate antimicrobial therapy. Pro-

spective studies are needed to investigate this issue further, as well as the role of allergy and possible immune dysfunction in children with chronic sinus disease.

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Rhegmatogenous Retinal Detachment Following Cryotherapy in Retinopathy of Prematurity

Craig M. Greven, MD, William Tasman, MD (*Arch Ophthalmol.* 1989;107:1017-1018)

Sex Steroids Do Not Influence Somatic Growth in Childhood

Susana P. Campos, MD, Margaret H. MacGillivray, MD

• The influence of sex steroids on somatic growth during childhood was evaluated by reviewing linear growth characteristics of 18 agonadal patients with normal sex chromosomes. None of the heights throughout childhood and before the onset of sex steroid therapy were below 2 SDs of the mean. Based on the normal z scores of these patients, we concluded that somatic growth throughout the childhood and prepubertal years is not sex-steroid dependent.

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Previous studies have evaluated the growth-promoting effects of androgens, estrogens, and/or growth hormone treatment in girls with Turner syndrome. Recently, the efficacy of low doses of estradiol was assessed in patients with Turner syndrome who were as young as 5 years of age.¹ Estrogen treatment of these young girls was based on clinical observations that linked the growth spurt of girls with normal karyotype to small increments in estrogen production during early puberty and to the assumption that estrogen deficiency in girls with Turner syndrome might play a role in their growth deceleration during childhood.

We examined the influence of sex steroids on somatic growth during childhood by evaluating the linear growth characteristics of 18 anatomically or functionally agonadal patients with normal sex chromosomes. Based on their growth patterns, we concluded that somatic growth throughout the childhood and prepubertal years is not dependent on gonadal estrogens or androgens.

PATIENTS AND METHODS

The linear growth charts of 18 anatomically or functionally agonadal patients with structurally normal sex chromosomes were reviewed. Each patient's assigned sex, clinical diagnosis, karyotype, age at laparotomy and/or gonadectomy, gonadotropin levels, age, and height in SD scores (z scores) at the

onset of sex steroid replacement are given in the Table. The various causes of agonadism included gonadal agenesis, gonadal dysgenesis, vanishing testes syndrome, surgical gonadectomy in infancy for intersex problems, gonadal destruction from radiation and chemotherapy for primary malignancy, and biosynthetic defect in sex steroid production (17 α -hydroxylase deficiency). The agonadal state was confirmed in infancy and early childhood by exploratory laparotomy, low plasma sex steroid concentrations, and/or elevated plasma gonadotropin levels.

In four patients (patients 3, 5, 9, and 12), the agonadal state was confirmed after surgical exploration at a relatively advanced age (15 years 7 months, 15 years 3 months, 14 years 6 months, and 10 years, respectively). Patient 3 was referred at age 13 years for delayed adolescence. The plasma follicle-stimulating hormone (FSH) level exceeded 50 IU/L (normal, <10 IU/L). Plasma luteinizing hormone (LH) level was 25.1 IU/L (normal, 2 to 6 IU/L), and her vaginal smear showed no estrogen effect. Streak gonads were removed at the time of laparotomy. Patient 5 was first seen at age 15 years 6 months for delayed sexual development. The plasma gonadotropin level was elevated (FSH, 47.7 IU/L; LH, 12.9 IU/L), and there was no estrogen effect on vaginal smear. On laparoscopy, one gonad was absent and the other was atrophic. Patient 9 was evaluated at 8 months of age for micropenis and small, soft, retractile testes. He was not available for follow-up and returned at age 14 years 10 months after having undergone bilateral inguinal exploration, bilateral orchidopexy, and insertion of testicular prostheses. Histopathologic evaluation revealed atrophic testes. Plasma FSH level was less than 1.0 IU/L, LH level was 6.6 IU/L, and testosterone level was 1.6 nmol/L (normal adult male level, 140 to 280 nmol/L). A gonadotropin-releasing hormone test revealed gonadotropin deficiency. Patient 12 presented at age 15 years 1 month with micropenis and undescended testes. He had undergone abdominal and inguinal exploration at age 10 years and no gonads were found. Plasma FSH level was 46 IU/L, plasma LH level was 21.0 IU/L, and serum testosterone level was 0.8 nmol/L.

Patients 4 and 9 were unusual in that they had atrophic testes and severe gonadotropin deficiency. Patient 4 had severe micropenis with palpable erectile tissue being only 4 to 5 mm. She underwent bilateral gonadectomy and female sex reassignment at age 1 year 3 months. The plasma FSH level was 2.0 IU/L and LH level was 1.0 IU/L before sex steroid

replacement. Patient 9 was discussed previously. They are included in this study because they had nonfunctional gonads and absence of sex steroids. They are not representative of the usual patients with gonadotropin deficiency whose testes are responsive to gonadotropin replacement.

Twelve patients were raised as females: seven of these had a 46,XY karyotype and five had a normal 46,XX karyotype. Absence of sex steroids in these patients was confirmed by either low plasma estradiol level (<73.4 pmol/L) and/or absence of estrogen effect on vaginal mucosal smears. The six phenotypic males all had a normal 46,XY karyotype and low plasma testosterone levels (0.4 to 1.6 nmol/L) associated with either documented vanishing testes syndrome or atrophic testes. Five of the patients (patients 1, 2, 12, 15, and 18) had the syndrome of vanishing testes. All these individuals had a small but normally formed penis and empty scrotal sacs. Elevated gonadotropin levels and very low gonadal steroids were measured before replacement treatment, making a human chorionic gonadotropin stimulation test unnecessary. Nevertheless, patients 2, 15, and 18 had had a human chorionic gonadotropin stimulation test done, which showed no rise in plasma testosterone level.

The age range at onset of sex steroid replacement was 11 years 5 months to 15 years 8 months; none of the patients had received sex steroid treatment before starting replacement therapy. We chose to evaluate the growth of our patients on the basis of their sex of rearing because somatic growth during childhood does not appear to be dependent on genetic sex; the Figure illustrates that the growth curves of boys and girls are almost identical during this period.

RESULTS

None of the 18 patients had heights and growth percentiles that were below 2 SDs of the mean for normal children (Figure). The z scores at initiation of sex steroid therapy ranged from -1.22 to 2.06 (Table). Sex steroid replacement was begun at a chronologic age compatible with normal puberty and resulted in the expected physiologic growth spurt (Figure). Historical information on parental heights was available in 7 of 11 adult patients. The final adult heights of these patients closely approximated or exceeded the midparental height.

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Clinical Data on 18 Agonadal Children

Patient/Sex of Assignment	Diagnosis	Karyotype	Age at Gonadectomy/Laparotomy*	Plasma FSH/LH at Onset of Sex Steroid Therapy, IU/L†	Age at Onset of Sex Steroid Therapy	Height in SD Units (z Score) at Onset of Sex Steroid Therapy
1/M	Vanishing testis syndrome	46, XY	2 y 9 mo	50/6.6	11 y 7 mo	+0.377
2/M	Vanishing testis syndrome	46, XY	3 y	58.1/9.3	11 y 8 mo	+0.549
3/F	Streak gonads	46, XX	15 y 3 mo	50/25.1	15 y 3 mo	-0.583
4/F	Testicular agenesis	46, XY	1 y 3 mo	2.0/1.0	12 y 4 mo	-0.301
5/F	Dysgenetic gonad	46, XX	17 y 3 mo	47.7/12.9	15 y 8 mo	-0.633
6/F	Androgen insensitivity	46, XY	4½ mo	22.9/7.8	12 y	1.493
7/F	Neuroblastoma status post chemotherapy and radiation therapy	...	2 y 6 mo	76/74	11 y 11 mo	1.477
8/F	Agenesis of the penis	46, XY	6 d	32.7/6.9	11 y 6 mo	0.436
9/M	Atrophic testes	46, XY	14 y 6 mo	1.0/6.6	15 y 1 mo	-0.561
10/F	17 α -hydroxylase deficiency	46, XY	13 y 9 mo	...	13 y 9 mo	0.867
11/F	17 α -hydroxylase deficiency	46, XX	...	50/24	13 y 9 mo	-1.80
12/M	Vanishing testis syndrome	...	10 y	46/21	15 y 7 mo	-1.20
13/F	Testicular dysgenesis	46, XY	4 mo	...	11 y 6 mo	0.436
14/F	Wilms' tumor status post chemotherapy and radiation therapy	...	4 y 9 mo	46.2/21.2	15 y 9 mo	-0.967
15/M	Vanishing testis syndrome	...	5 y	34.6/9.2	13 y 3 mo	1.786
16/F	Probable androgen insensitivity	46, XY	14 mo	43/9.3	11 y 4 mo	-1.22
17/F	Androgen insensitivity	46, XY	2½ mo	83.7/21.9	11 y 11 mo	2.064
18/M	Vanishing testis syndrome	46, XY	3 y	57/13.5	12 y 11 mo	0.756

*Absence of gonads was established at laparotomy in patients 1, 12, 15, and 18.

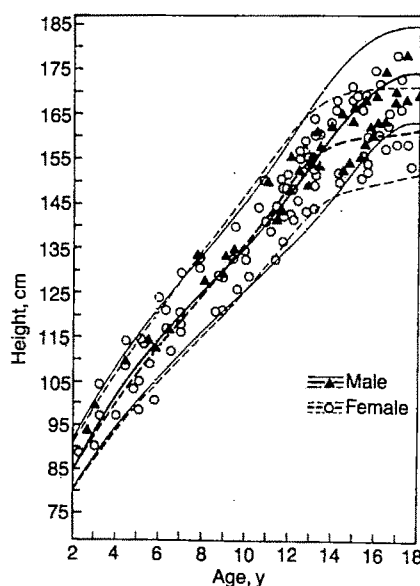
†Normal follicle-stimulating hormone (FSH) level is less than 10 IU/L and normal luteinizing hormone (LH) level is 2 to 6 IU/L.

COMMENT

The normal linear growth patterns observed in our agonadal children suggest that gonadal steroids do not influence somatic growth during childhood. Although the agonadal state was documented at a relatively advanced stage in four of the patients (patients 3, 5, 9, and 12), the pathologic examination of their gonads indicated that they had congenitally nonfunctional gonads. Two of the patients (patients 10 and 11) had a total lack of gonadal steroids due to a congenital 17 α -hydroxylase deficiency. The remainder of the patients had gonadectomy performed in their early childhood years.

All 5 patients who were started on sex steroid therapy at 15 years of age or later had a slightly negative z score. Only 3 of the 13 remaining patients in whom steroid therapy was initiated between ages 11 to 13 years had negative z scores. Although it appears that age at initiation of sex steroid therapy influences the z score, no patient regardless of the age of onset of sex steroid replacement had a z score that was below 2 SDs of the mean.

Based on these observations, it is highly unlikely that estrogen defi-



All available heights of phenotypic male and female patients plotted on the normal growth percentiles (5th, 50th, 95th) for male and female patients.

ciency is responsible for the childhood growth failure of girls with Turner syndrome. More likely, loss of growth-regulating genes on the short arm of the X chromosome (Xp) and possibly an in-born difference in skeletal growth are etiologic factors.

Estrogen treatment in girls with Turner syndrome has been initiated at an increasingly young age.^{1,2} Previous studies suggest that the growth-promoting effects of estrogen therapy in Turner syndrome are not sustained beyond 12 to 24 months,^{3,4} and long-term adverse effects of estrogen on bone maturation and adult height have been reported in these patients.⁵ Since sex steroids do not play a role in somatic growth during the first decade of life, we recommend that estrogen treatment of girls with Turner syndrome be initiated at a chronological age that is compatible with onset of normal puberty.

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Increased Phagocytic Cell Chemiluminescence in Patients With Cystic Fibrosis

Robert L. Roberts, MD, PhD, E. Richard Stiehm, MD

• The oxidative burst of polymorphonuclear cells and monocytes from patients with cystic fibrosis as measured by luminol-enhanced chemiluminescence was examined after *in vitro* activation of the cells. All patients were outpatients at the time of the assays; their median age was 25.5 years (range, 12 to 33 years) and normal controls were young healthy adults. Stimulation of polymorphonuclear cells with phorbol myristate acetate, the chemotactic peptide *N*-formyl-methionyl-leucyl-phenylalanine, and the calcium ionophore A23187 resulted in significantly greater chemiluminescence responses from the cells of patients than from the control cells. The monocyte response of patients to opsonized zymosan was also greater than that of controls. Thus, phagocytic cells from adolescents and young adults with cystic fibrosis have a greater chemiluminescence response to a variety of stimuli. This may result in tissue damage in the lungs of these patients and thus make them more susceptible to pulmonary infections.

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Pulmonary infections account for the majority of deaths in cystic fibrosis (CF), but patients with CF have little difficulty containing infections outside the respiratory tract. The ability to mount normal systemic immune responses suggests that the respiratory host defense mechanisms of patients with CF may be defective, evidenced by continued colonization of bacteria in the lungs despite antibiotic therapy.

Phagocytic cells, alveolar macrophages, and polymorphonuclear leukocytes (PMNs) in the normal lung are

able to prevent the colonization of bacteria that enter the lower airways. These phagocytic cells are present in large numbers in the lungs of patients with CF,¹ thus making a chemotactic defect an unlikely cause for their increased susceptibility. After the bacteria have been opsonized and ingested, they are killed by the release into the phagolysosome of reactive oxygen intermediates (ROIs), proteolytic enzymes, and other antimicrobial agents from the phagocyte. These ROIs and proteolytic enzymes from the phagocyte may also injure host tissues, which has been documented to occur in adult respiratory distress syndrome²⁻⁵ and in experimental models of inflammatory lung disease.⁶⁻⁸

Fick et al^{9,10} have shown that immunoglobulins specific for *Pseudomonas aeruginosa* are present in the bronchoalveolar lavage fluid of patients with CF. However, up to 80% of the IgG *Pseudomonas* antibody in the bronchoalveolar lavage of patients with CF had been degraded into Fab and Fc fragments, which inhibit phagocytosis of the bacteria by pulmonary alveolar macrophages. Fragmentation of immunoglobulin molecules may be promoted by the release of proteolytic enzymes and ROIs from phagocytic cells.¹¹⁻¹³ Thus, increased phagocytic cell activity in the lungs may damage protective antibodies and allow bacterial colonization to occur.

In the present study, PMNs and monocytes from patients with CF were studied for their ability to release ROIs as measured by chemiluminescence. The effects of extracellular calcium on these responses were also examined. The phagocytic cells of patients with CF were found to have significantly increased chemiluminescence activity for all stimuli tested compared with age-matched controls in the presence or absence of extracellular calcium. The excessive release of ROIs from the

phagocytic cells of patients with CF may impair local host defenses in the lungs and result in pulmonary infections.

MATERIALS AND METHODS

Patient Population

Patients with CF were identified from among the outpatient population treated at the Cystic Fibrosis Center at UCLA in accordance with the University of California Human Subjects Protection Committee. The majority of the patients treated at this clinic are older adolescents and young adults. The total study population had a median age of 25.5 years and a mean age (\pm SEM) of 23.6 ± 1.3 years with a range of 12 to 33 years. All patients had positive sputum cultures for *P. aeruginosa* and the results of their pulmonary function tests, complete blood cell counts, and erythrocyte sedimentation rates were recorded. Most of the patients were receiving some form of oral or inhaled antibiotic at the time of the assay. Patients who were severely ill and who required hospitalization were not included in the study population. Normal volunteers were in good health and had an age range of 21 to 38 years.

Materials

All reagents were obtained from Sigma Chemical Co, St Louis, Mo, except for polyvinylpyrrolidone-treated silica (Percoll, Pharmacia Fine Chemicals, Piscataway, NJ) and 5-amino 2,3 dihydro 1,4 phthalazinedione (luminol, Eastman Kodak, Rochester, NY).

All water-insoluble compounds were dissolved in dimethyl sulfoxide to make appropriate stock solutions so that the final concentration of dimethyl sulfoxide in the reaction mixtures was 0.01% or less, a concentration not found to affect any of the assays performed or the viability of cells as measured by trypan blue dye exclusion or lactate dehydrogenase release.

Opsonized zymosan was prepared by incubating zymosan particles in fresh normal human serum (15 mg/mL) for 30 minutes at 37°C in a rocking water bath followed by washing in phosphate-buffered saline solution and then resuspending in HEPES buffer.

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Buffer solutions were prepared by using Hanks balanced saline solution, which includes 1.6 mmol of calcium chloride, 0.2 mmol of magnesium sulfate, 0.1 mmol of magnesium chloride, and 11 mmol of glucose, and buffered with 10 mmol of HEPES adjusted to pH 7.35. In some experiments, calcium and magnesium were omitted from the buffer.

Separation of PMNs

Peripheral blood obtained from normal volunteers and patients by venipuncture was anticoagulated with ethylenediamine tetraacetic acid (EDTA; 0.3% final concentration). The PMNs from both the control and the patient were separated simultaneously on discontinuous Percoll gradients.¹⁴ The Percoll gradients were prepared by diluting Percoll with a density of 1.130 (referred to as 100%) with concentrated ($\times 10$) phosphate-buffered saline solution to obtain an osmolality of 310 to 320 mOsm/kg and then further diluting with $\times 1$ phosphate-buffered saline solution to obtain Percoll concentrations of 62.5% and 75%. A 3-mL volume of the 62.5% solution was placed in a 15-mL conical tube (Falcon 2095, Oxnard, Calif), and then 3 mL of the 75% Percoll was layered below the 62.5% layer by means of a narrow catheter placed at the bottom of the tube. Whole blood (4 mL) that had been diluted 50% with $\times 1$ phosphate-buffered saline solution was then layered over the Percoll gradient. The tubes were centrifuged at 1500 rpm (400g) at 22°C for 25 minutes, resulting in the formation of one band of leukocytes above the 62.5% layer (band I) and another between the 62.5% and 75% layers (band II). Band II was composed predominantly of neutrophils (96% to 99%), with the remainder of cells being eosinophils (1% to 4%) or lymphocytes (0% to 1%). The erythrocytes pelleted to the bottom of the tube, and hypotonic lysis was required to remove residual erythrocytes from band II. The cells were washed twice in phosphate-buffered saline solution and stained with Wright's stain to identify different cell types.

Separation of Monocytes

Separation of monocyte populations also employed Percoll gradients. Whole blood from normal volunteers and patients was anticoagulated with EDTA, diluted 50% with phosphate-buffered saline solution, and concentrated ($\times 10$) phosphate-buffered saline solution was added to increase the osmolality by 60 mEq, which preferentially increased lymphocyte density.¹⁵

The blood was incubated at 37°C for 30 minutes to increase the density of the lymphocytes and thus allow for their separation from monocytes. The blood was then layered over isotonic Percoll (48%) in a 15-mL conical tube. The tubes were spun at 1500 rpm for 25

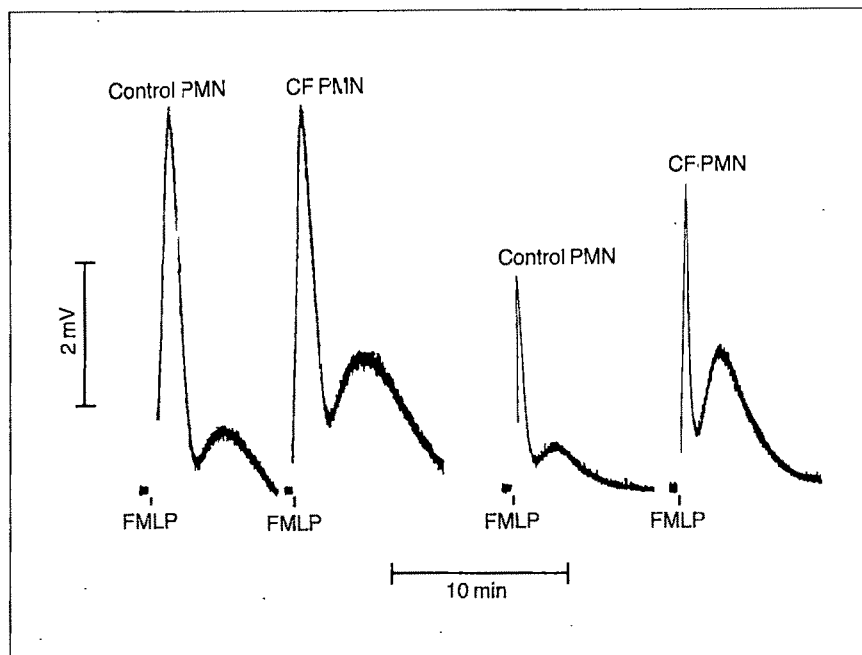


Fig 1.—Luminometer tracings of chemiluminescence response of polymorphonuclear leukocytes (PMNs) from controls and patients with cystic fibrosis (CF) in response to *N*-formyl-methionyl-leucyl-phenylalanine (FMLP) (10^{-6} mol/L). The cells were tested in the presence (left) and absence (right) of extracellular calcium. There was a 10-minute preincubation at 37°C with cytochalasin B (5 mg/L) before adding FMLP. There was no detectable chemiluminescence response before stimulation at this luminol concentration at these luminometer settings (full scale, 10 mV).

minutes at 22°C, and the resulting cell layer above the Percoll was collected and washed twice in phosphate-buffered saline solution. The cells were $90.0\% \pm 1.0\%$ esterase positive, and $85.8\% \pm 3.8\%$ were monocytes by Wright staining. The remainder of the cells were lymphocytes and less than 1.0% neutrophils. The yield of recovered monocytes was greater than 60%.

Chemiluminescence

Assays for chemiluminescence were done on the LKB 1250 luminometer (LKB-Wallac, Turku, Finland) at 37°C with full scale representing 10 mV. Cells (10^6) were suspended in 1 mL of HEPES buffer containing calcium, magnesium (unless otherwise stated), and luminol (10^{-6} mol/L for PMNs and 10^{-6} mol/L for monocytes). Preliminary experiments had shown that this cell concentration (10^6 /mL) gives maximal chemiluminescence response per cell. Cells were incubated for 10 minutes at 37°C before adding any stimuli. The peak (or peaks for biphasic responses) was recorded in millivolts, and the time to reach the peak was also noted.

Statistical Analysis

A Student *t* test (two-tailed, paired) was used to compare the means (\pm SEMs) of different variables.

RESULTS

PMN Chemiluminescence

Typical tracings of the chemiluminescence responses of PMNs in normal controls and in patients with CF to the chemotactic peptide *N*-formyl-methionyl-leucyl-phenylalanine (FMLP) (10^{-6} mol/L), both in the presence and absence of extracellular calcium as recorded by the luminometer, are shown in Fig 1. All of the cells had been preincubated in cytochalasin B (5 mg/L), which greatly enhances the chemiluminescence response to FMLP. The PMNs in normal controls and patients with CF in the presence or absence of calcium display a biphasic response to FMLP with a rapid first peak that is reached in 40 to 60 seconds, followed by a later second peak at 4 to 6 minutes. It is also apparent that there is a greater decrease in the first peak of normal PMNs than in PMNs of patients with CF when calcium is absent.

Figure 2 (left) compares both the first and second mean peak chemiluminescence responses to FMLP for PMNs from controls and patients ($n = 16$ deter-

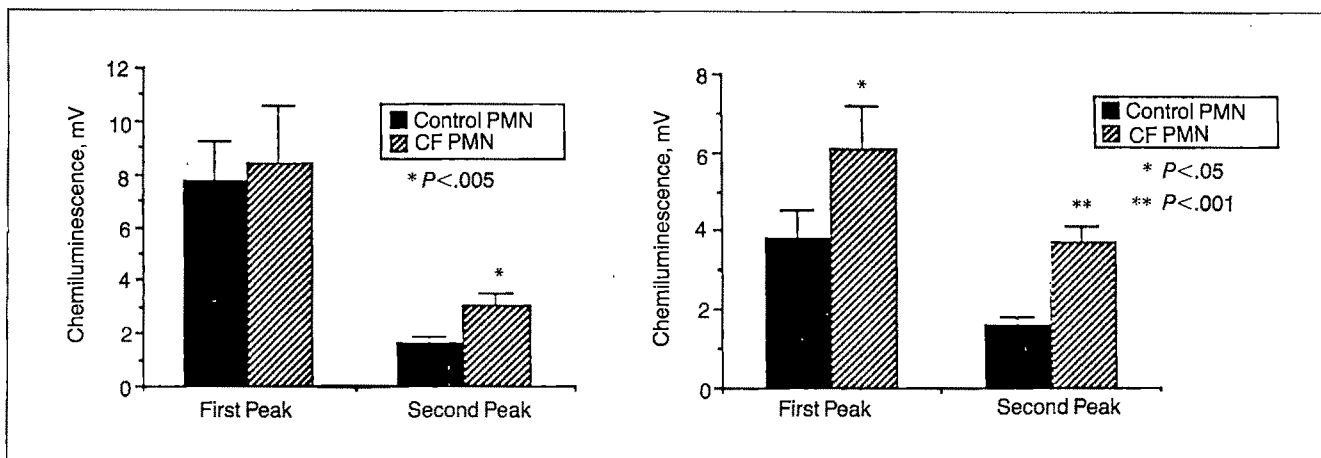


Fig 2.—Mean peak chemiluminescence responses of polymorphonuclear leukocytes (PMNs) from controls and from patients with cystic fibrosis (CF) to *N*-formyl-methionyl-leucyl-phenylalanine (FMLP) (10^{-6} mol/L) in the presence (left) and absence (right) of extracellular calcium. The cells had been preincubated in cytochalasin B (5 mg/L) for 10 minutes at 37°C addition of *N*-formyl-methionyl-leucyl-phenylalanine. See Fig 1 and text for explanation of how first and second peaks are defined.

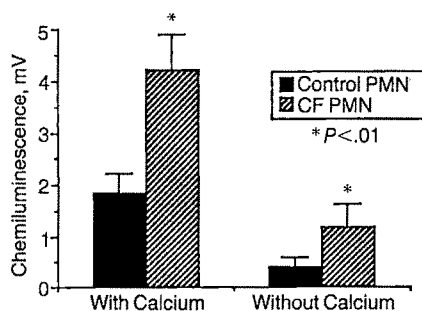


Fig 3.—Mean chemiluminescence peak responses of polymorphonuclear leukocytes (PMNs) from controls and patients with cystic fibrosis (CF) to the calcium ionophore A23187 (10^{-5} mol/L) in the presence and absence of extracellular calcium. The cells had been preincubated in cytochalasin B (5 mg/L) for 10 minutes at 37°C before A23187 was added. The luminol concentration was increased to 10^{-5} mol/L ($\times 10$) in cells tested in the absence of calcium due to their decreased chemiluminescence response.

minations with two patients repeated on different days). The cells had been preincubated in cytochalasin B with calcium (1.6 mmol) present. No difference between PMN responses of normal controls and of patients with CF for the first peak was noted (7.77 ± 1.49 mV for controls; 8.45 ± 2.16 mV for patients with CF), but the second peak of levels of PMNs from patients with CF (3.04 ± 0.48 mV) was significantly greater ($P<.005$) than that of the PMNs of normal controls (1.61 ± 0.26 mV). There was no difference between PMN

responses of normal controls and patients with CF in the time required to reach the second peak (5.00 ± 0.29 minutes for normal controls; 5.03 ± 0.27 minutes for patients with CF).

Figure 2 (right) compares the peak chemiluminescence responses of PMNs from normal controls and in patients with CF in the absence of extracellular calcium ($n=21$ with two patients repeated on different days). The first peak, reflecting activation at the membrane binding level,¹⁶ is decreased by the absence of calcium for both the normal and patient PMNs, but the patient response (6.10 ± 1.09 mV) was greater than that of controls (3.83 ± 0.68 mV; $P<.05$). The second chemiluminescence peak in response to FMLP represents intracellular activity and is myeloperoxidase dependent.¹⁷ The absence of calcium did not decrease the magnitude of the second peak and actually increased the difference between the responses of patients with CF and normal controls (3.70 ± 0.43 mV for patients with CF; 1.61 ± 0.21 mV for normal controls; $P<.001$). Similar results to those performed in the absence of calcium are obtained if EDTA (1 mmol) is present (not shown), indicating that little extracellular calcium is available to the cells. Altering the magnesium concentration did not produce any additional differences in chemiluminescence responses of PMNs from normal controls and pa-

tients with CF.

Stimulation of PMNs with the calcium ionophore A23187 produces a single chemiluminescence peak, and results for patients and controls are shown in Fig 3 ($n=16$ with three patients tested on different days). The cells had been preincubated in cytochalasin B (5 μ g/mL), which enhances the response to the ionophore. The peak chemiluminescence responses of PMNs in patients with CF were greater than that of the controls in either the presence (4.21 ± 0.68 mV for patients with CF; 1.85 mV ± 0.38 mV for normal controls; $P<.005$) or absence (1.21 ± 0.42 mV for patients with CF; 0.40 ± 0.18 mV for normal controls; $P<.01$) of calcium. The time required to reach the peak response to A23187 was not different for PMNs from normal controls and from patients with CF (2.53 ± 0.51 minutes for normal controls; 3.18 ± 0.70 minutes for patients with CF).

The chemiluminescence response of normal and patient PMNs to phorbol myristate acetate (20 ng/mL) was also tested. These cells were tested in the presence of calcium although phorbol myristate acetate directly activates protein kinase C and is not strictly dependent on extracellular calcium.¹⁸ The peak response was 10.2 ± 2.2 mV for the normal PMNs and 15.2 ± 1.9 mV for the patient PMNs ($P<.001$; $n=23$ with three patients tested on different days).

The time required to reach the peak response to phorbol myristate acetate was not different for PMNs from normal controls and patients with CF (4.85 ± 0.32 minutes for normal controls; 4.94 ± 0.34 minutes for patients with CF). The results of these chemiluminescence experiments are summarized in Table 1.

Monocyte Chemiluminescence

Monocytes in normal controls and in patients with CF were stimulated with serum-opsonized zymosan in the presence or absence of calcium (Fig 4). The chemiluminescence response of monocytes is similar to that of PMNs to FMLP in that there is a rapid first peak reached within 40 to 60 seconds followed by a second peak or plateau at 4 to 6 minutes. In the absence of calcium (Fig 4), the first peak is barely detectable for normal monocytes. The first peak is also diminished in the patient monocytes in the absence of calcium but is still prominent compared with the tracings of normal monocytes.

Figure 5 shows the peak chemiluminescence responses for both the first and second peaks for the monocytes of normal controls and of patients with CF in the presence (left) and absence (right) of extracellular calcium ($n=9$). The patient monocyte response in the presence

of calcium was greater than that of normal monocytes for both the first peak (3.91 ± 0.97 mV for normal controls; 12.28 ± 2.8 mV for patients with CF; $P<.005$) and the second peak (2.20 ± 0.46 mV for normal controls; 6.20 ± 1.22 mV for patients with CF; $P<.005$). The chemiluminescence responses for monocytes of normal controls and patients with CF were lower in the absence of calcium, but the relative differences for both the first peak (0.29 ± 0.07 mV for normal controls; 1.89 ± 0.42 mV for patients with CF; $P<.005$) and the second peak

(1.33 ± 0.52 mV for normal controls; 4.45 ± 1.09 mV for patients with CF; $P<.01$) were greater.

COMMENT

The PMNs and monocytes from patients with CF released greater amounts of ROI as measured by chemiluminescence after stimulation with a variety of agents. Other investigators have also examined the oxidative potential of phagocytes from patients with CF, as noted in Table 2. Graft et al¹⁹ compared the chemiluminescence response to zymosan of PMNs from nor-

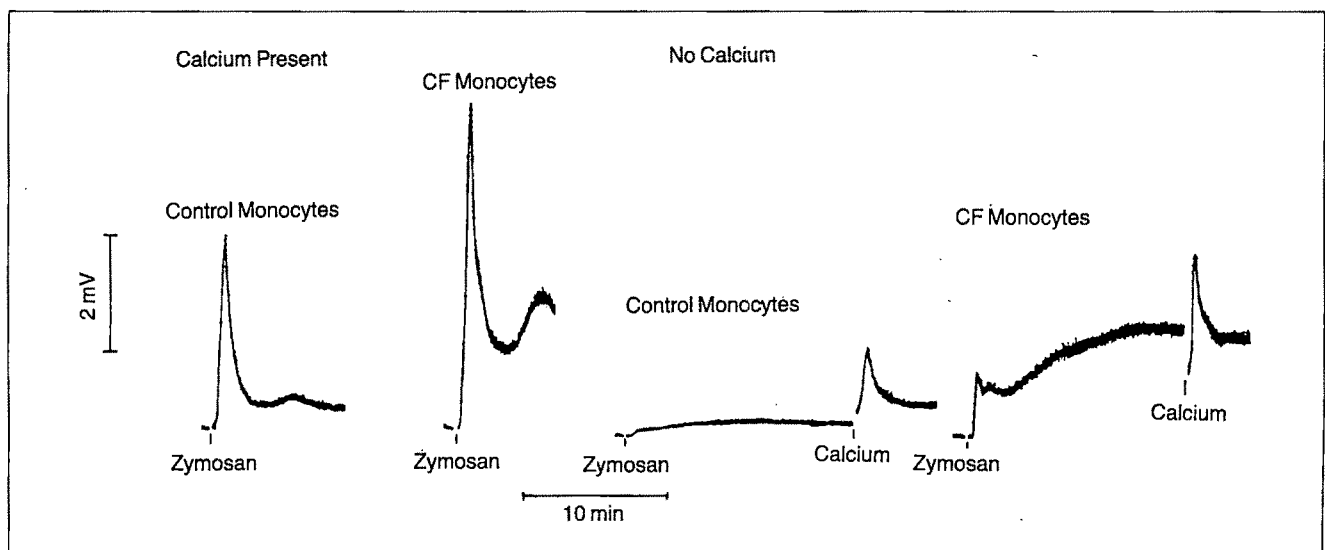
Table 1.—Peak Chemiluminescence Responses of Polymorphonuclear Leukocytes*

Stimuli	Normal Controls, mV	Patients With CF, mV	P
FMLP with calcium†			
First peak	7.77 ± 1.49	8.49 ± 2.16	NS
Second peak	1.61 ± 0.26	3.04 ± 0.48	<.005
FMLP without calcium†			
First peak	3.83 ± 0.68	6.10 ± 1.09	<.05
Second peak	1.61 ± 0.21	3.70 ± 0.43	<.001
Calcium ionophore†			
With calcium	1.85 ± 0.38	4.21 ± 0.68	<.005
Without calcium	0.40 ± 0.18	1.21 ± 0.42	<.01
PMA with calcium	10.2 ± 2.2	15.2 ± 1.9	<.001

*Results are given as mean \pm SEM. CF indicates cystic fibrosis; FMLP, N-formyl-methionyl-leucyl-phenylalanine; PMA, phorbol myristate acetate; and NS, not significant.

†Cells had been preincubated in cytochalasin B (5 mg/L).

Fig 4.—Luminometer tracings of chemiluminescence response of monocytes from controls and patients with cystic fibrosis (CF) to serum opsonized zymosan in the presence and absence of extracellular calcium. Calcium (1.6 mmol/L) was added to cells after peak response in absence of calcium had been reached.



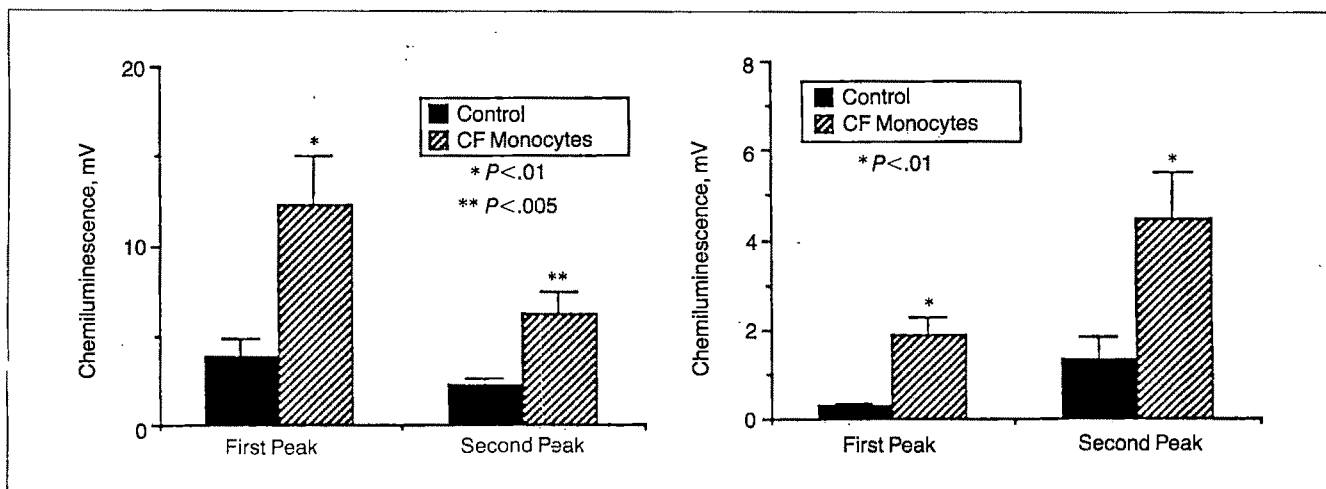


Fig 5.—Mean peak chemiluminescence responses of monocytes from controls and patients with cystic fibrosis (CF) to opsonized zymosan in the presence (left) and absence (right) of extracellular calcium. The cells had been preincubated at 37°C for 10 minutes before zymosan was added. See Fig 4 and text for explanation of how first and second peaks are defined.

Table 2.—Comparison of Studies Examining Chemiluminescence Response of Leukocytes From Patients With CF*

Study	Age of Patients, y	Cell Type	Method†	General Responses‡
Graft et al, ¹⁹ 1982	15.3 ± 2.8	PMNs	Luminol	Normal to increased
Regelman et al, ²⁰ 1986	2-40§	Monocytes	Luminol	Normal to increased
Kemp et al, ²¹ 1986	15.2 ± 3.8	PMNs	Native chemiluminescence	Decreased to normal
Present study	23.6 ± 3.1	PMNs and monocytes	Luminol	Increased

*Results are given as mean ± SEM. CF indicates cystic fibrosis; PMNs, polymorphonuclear leukocyte cells.

†Method indicates methods for chemiluminescence assay, all of which were done at 37°C.

‡Patient with CF vs normal controls. See text for explanation.

§Values are given as range; means were not available.

mal controls with that in adolescents with CF (mean age, 15.3 ± 2.8 years) and found no difference in the height of the peak response. However, the peak response was reached more rapidly in the patients with CF. The authors concluded that PMNs were in a "primed" state in CF and did find a correlation between lower National Institute of Health, Bethesda, Md, clinical scores and a more rapid onset of the peak response. Regelman et al²⁰ compared the monocyte chemiluminescence responses of controls, of carriers of the gene for CF (obligate heterozygotes), and of patients with CF (aged 2 to 40 years). They found no differences in the chemiluminescence response to zymosan or phorbol myristate acetate but did find

that the adherence-stimulated chemiluminescence responses of the carriers and patients were significantly greater than those of controls. Kemp et al²¹ found a decreased chemiluminescence response and lysosomal enzyme release from PMNs of patients with CF when stimulated by FMLP but no difference between PMNs in patients with CF and normal controls when enzyme release was stimulated by calcium ionophore or opsonized zymosan.

Our results differ from these studies in that we found that both PMNs and monocytes from patients with CF were more active than those in controls for most of the stimuli tested. These differences may be due in part to the fact that our patient population was almost 10

years older than patients in the other studies (Table 2). If the propensity for enhanced phagocytic cell activity is an intrinsic property in CF (as suggested by Regelman²⁰), then cells from these patients may become more activated or "primed" by chronic infections as the patient gets older. Bacterial infections have been shown to increase the oxidative activity of PMNs in diseases other than CF.²²⁻²⁴ Patients with CF also develop circulating immune complexes as the disease progresses, and these complexes may also activate PMNs and monocytes.^{25,26}

Kemp et al²¹ found a decreased response of PMNs from patients with CF in contrast to the other three studies (Table 2). The study by Kemp et al also differs from the three other studies in that luminol was not used to enhance the chemiluminescence response. Kemp and colleagues instead used a liquid scintillation counter to measure "native" chemiluminescence, which is primarily dependent on superoxide release from the PMNs.²⁷ Luminol-enhanced chemiluminescence is dependent on myeloperoxidase and the formation of hypohalous acid and other ROIs.²⁸⁻³⁰ Thus, one difference between the Kemp et al study and the others is that different ROIs are being measured as they are released from the cells (Table 2). This may indicate that PMNs and monocytes from patients with CF release relatively more myeloperoxidase-depen-

dent ROIs than they do other ROIs.

The increased release of myeloperoxidase-dependent, halogenated oxidants as measured by luminol-enhanced chemiluminescence has potentially important clinical significance due to the greater toxicity of halogenated ROIs. Hypochlorous acid is the predominant halogenated product of neutrophils, whereas eosinophils preferentially generate hypobromous acid at physiologic concentrations of bromide.³¹ Hypochlorous acid is able to oxidize membrane lipids and proteins, leading to cell death.³² The α_1 -proteinase inhibitor that protects lung tissues from excessive elastase-mediated tissue damage may be inactivated by exposure to hypochlorous acid or long-lived nitrogen-chloride derivatives.³³ Chlorinated ROIs may also activate latent neutrophil collagenase and lead to further tissue damage.³² Hypochlorous acid can also cross-link immune complexes, making the immune complexes long-lived and enhancing their inflammatory properties.³⁴ Alginic acid purified from *P aeruginosa* has the ability to scavenge hypochlorous acid, thus protecting the *Pseudomonas* organism that may have particular relevance to CF.³⁵

All of the CF subjects in the present study were ambulatory outpatients at the time of test results, although most already had some degree of respiratory impairment evidenced by decreased pulmonary function testing, and all were colonized with *P aeruginosa*. No correlation between the phagocytic chemiluminescence responses and the decrease in pulmonary functions has as yet been noted in our study. A negative correlation was found, however, between the erythrocyte sedimentation rates and pulmonary functions of patients with CF (forced vital capacity, $r = -.912$ and $P < .01$; forced expiratory volume in 1 second, $r = -.951$ and $P < .001$), suggesting that the patient's clinical status worsens as the inflammatory processes within the lungs increase. A longer study with a larger number of patients with CF may be necessary to determine what effect factors such as initial colonization with *Pseudomonas*, age, and acute illness have on phagocyte oxidative responses.

The increased release of ROIs from phagocytosis cells is also suspected to

play a damaging role in many other diseases, such as rheumatoid arthritis and inflammatory bowel disease. We have found in an unrelated study that monocytes from patients requiring hyperalimentation for inflammatory bowel disease had a chemiluminescence response to opsonized zymosan that is more than twice the response of normal controls or patients requiring hyperalimentation without inflammatory bowel disease.³⁶ Others^{37,38} have also found increased oxidative responses from both monocytes and alveolar macrophages from patients with inflammatory bowel disease. Thus, although the cause of CF and these diseases differs, the generation of phagocytic cells with increased potential to release ROIs may perpetuate the inflammatory response, whether in the lung or the bowel, and exacerbate the disease process.

Several studies have demonstrated abnormalities in calcium flux or calcium levels in the cells of patients with CF.³⁹⁻⁴² Increased levels of cytosolic calcium have been reported in patient PMNs and mononuclear cells,^{43,44} but Suter et al⁴⁵ did not find differences in cytosolic calcium when patient and normal neutrophil levels were compared. Waller et al⁴⁶ did find that total cell calcium was greater in lymphocytes from patients with CF, although the cytosolic calcium levels were the same as controls. Increased chemiluminescence production of the patient cells in the absence of calcium in our study may indicate an abnormality in calcium metabolism or may reflect that these cells are in a "primed" state and need less calcium for activation. Kemp et al²¹ did find that PMNs in patients with CF were more resistant than PMNs in normal controls to calcium antagonists in regard to inhibition of β -glucuronidase release in response to FMLP stimulation.

Chronic inflammation may increase the calcium content of PMNs, as noted in a study of patients with rheumatoid arthritis whose total calcium content of their PMNs was increased fivefold compared with normal PMNs.⁴⁷ The authors also found that oral prednisone therapy resulted in a decrease in the calcium content of the PMNs in these arthritic patients.

Auerbach et al⁴⁸ found in a 4-year double-blind study that patients with CF

who were receiving alternate-day prednisone had increased growth, better pulmonary functions, and fewer hospitalizations than patients not receiving corticosteroids. Although corticosteroids may influence many factors affecting the clinical status of patients, the improvement of patients with CF who are receiving prednisone may indicate that the increased inflammatory response rather than progressive infection due to impaired immunity is responsible for the pathologic lung condition in CF. The clinical significance of this exaggerated inflammatory response appears to be limited to the lungs in CF, although patients with CF have developed leukocytoclastic vasculitis associated with exacerbations of their pulmonary disease.^{49,50}

Increased phagocytic cell activity could be damaging to the patients with CF by the destruction of protective antibodies in the lungs as previously discussed.^{9,13,51} High serum immunoglobulin levels have paradoxically been associated with an adverse outcome in CF. Patients with hypogammaglobulinemia and CF were found to have a better prognosis than those with normal or increased gamma globulin levels.^{52,53} Patients with higher titers of serum antibodies specific to *P aeruginosa* actually have worse pulmonary function and decreased survival compared with that in patients with lower titers.⁵⁴⁻⁵⁷ Circulating immune complexes that may increase the oxidative responses of PMNs have also been correlated with a worse clinical outcome in CF.^{58,59}

Thus, the propensity for pulmonary infections in CF is not due to a lack of specific immune responsiveness but may be due to the excessive inflammatory responses within the lungs.

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Gastroesophageal Reflux-Induced Hypoxemia in Infants With Apparent Life-Threatening Event(s)

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• To evaluate relationships between gastroesophageal reflux (GER) and the development and onset of apparent life-threatening event(s) (ALTE), 16 infants presenting with ALTE and 6 control subjects manifesting clinical GER alone were studied using prolonged, esophageal pH monitoring in conjunction with simultaneous pulse oximetry and transthoracic impedance pneumocardiography. Despite the absence of a clinical vomiting history in 14 of 16 patients with ALTE, the incidence of GER was similar in both groups (patients with ALTE vs control subjects, 95% vs 100%). Significant arterial oxygen desaturation ($<90\%$ for >3 minutes) was monitored during 60 episodes in 14 of 16 infants with ALTE, compared with no episodes of reduced arterial oxygen saturation in control subjects. Fifty-four of 60 of these desaturation events commenced within 3.9 ± 0.4 minutes (mean \pm SD) of onset of a drop in esophageal pH to less than 4.0. Linear regression analysis indicates a significant correlation between duration of esophageal acidification and length of individual hypoxemic episodes ($r = .39$). Pneumocardiograms were normal in all patients. These data suggest that unsuspected GER is common in infants presenting with ALTE and, in these patients, GER may be directly associated with reflex hypoxemic episodes. Prolonged intraesophageal pH monitoring, performed simultaneously with evaluation for apnea, should be considered in all infants presenting with ALTE.

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Gastroesophageal reflux (GER) has been implicated in the development and onset of infantile apnea. For example, esophageal pH monitoring, used in conjunction with pneumocardiography and nasal thermistor recording, has documented obstructive apnea occurring during GER episodes.¹⁻⁴ Recently, a newer classification of apneic syndromes of infancy, termed apparent life-threatening event(s) (ALTE), has been proposed.⁵ Previously referred to as "near-miss" sudden infant death syndrome, ALTE defines a symptom complex comprising apnea plus some combination of color change (ie, pallor, cyanosis, altered muscle tone, and choking or gagging).⁵ Episodes can occur while awake during the immediate or late postprandial period,¹ or onset of ALTE can present during sleep.⁶⁻⁸

Clinical follow-up studies suggest that infants with ALTE are at increased risk for development of sudden infant death syndrome. In infants presenting with ALTE, we have reported that a high percentage demonstrate significant GER,⁹ occurring both during sleep and in the immediate postprandial period, when evaluated according to previously established criteria.¹⁰⁻¹² Furthermore, GER is observed in a significant proportion of these patients despite the absence of a clinical history of regurgitation. To date, however, a precise relationship(s) between GER and ALTE has not been addressed. Accordingly, the aim of this study was to determine whether episodes of esophageal acidification in infants with ALTE are associated with abnormalities in cardiorespiratory function.

METHODS Study Groups

Characteristics of the patient population studied are shown in Table 1. From July 1,

1987, to December 31, 1987, 16 infants referred because of an ALTE episode were admitted to the Infant Apnea Center at Westchester County Medical Center, New York Medical College, Valhalla, NY, for evaluation. The patients were evaluated prospectively. Only 2 of 16 of these infants presented with a clinical history of vomiting/regurgitation. A group of contemporary control subjects was comprised of 6 age-matched infants with vomiting, resulting in poor weight gain and/or severe family disruption. None of the control subjects manifested symptoms associated with ALTE. All infants in both groups were products of full-term pregnancies with uneventful perinatal courses, including absence of chronic cough and/or wheezing.

Patient Evaluation

Complete blood cell counts and levels of serum electrolytes, blood urea nitrogen, creatinine, calcium, magnesium, and glucose as well as urinalysis results were within normal limits in all infants at the time of admission. Evaluation of infants with ALTE also included chest roentgenograms, electrocardiograms, echocardiography, 24-hour Holter monitoring, and electroencephalography. To assess relationships between esophageal acidification and cardiorespiratory function, all infants in both study groups underwent simultaneous 16- to 20-hour esophageal pH monitoring, continuous pulse oximetry, and transthoracic impedance pneumocardiography, according to the techniques described below.

Esophageal pH Monitoring.—Gastroesophageal reflux was evaluated using an ambulatory pH monitor (Biosearch Inc, Somerville, NJ), as we have described.¹³ Briefly, a 5F siliconized rubber catheter with a monocrystalline antimony pH electrode embedded at the tip, was passed through the nares and positioned in the distal esophagus according to the method of Strobel et al.¹⁴ To achieve esophageal acidification during oral feedings, unsweetened apple juice (300 mL/m², pH 3.5) was administered twice at 3-hour intervals, before resuming normal formula feeding.

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Table 1.—Clinical Presentation of Infants With Apparent Life-Threatening Event(s) (ALTE) and Control Subjects

Category	Patients With ALTE (n=16)	Control Subjects (n=6)
Age range, mo (mean \pm SD)	0.25-10.0 (2.4 \pm 0.6)	0.5-3.0 (2.0 \pm 0.5)*
Vomiting/regurgitation (%)	2/16 (12.5)	6/6 (100)†
Apnea and Pallor/cyanosis (%)	11/16 (68.8)	0/6 (0)†
Muscle-tone changes (%)	2/16 (12.5)	0/6 (0)†
Choking/gagging (%)	3/16 (18.8)	0/6 (0)†

*P = not significant.

†P < .001.

Table 2.—Intraesophageal pH and Oximetry Data Monitored For a Period of 16 to 20 Hours in Control Subjects and Infants With Apparent Life-Threatening Event(s) (ALTE)

	Patients With ALTE	Control Subjects	P
Gastroesophageal reflux episodes per patient, mean No.	28.8	26.5	NS*
Desaturation events (saturated oxygen <90% for >3.0 min) total No.	60	0	<.01
Events associated with esophageal pH <4.0, total No.	54	0	<.01
T-onset of oxygen desaturation following esophageal pH drop to <4.0, min (mean \pm SD)	3.9 \pm 0.4
T-duration of oxygen desaturation, min (mean \pm SD)	7.3 \pm 0.5

*NS indicates not significant.

For the purposes of this study, GER was defined as follows:

1. Immediate postprandial GER is indicated by a pH less than 4.0 during greater than 12 minutes of the initial 2 hours after feeding.¹⁰

2. Awake, delayed postprandial GER is indicated by a pH less than 4.0 persisting greater than 30 seconds in a minimum of 2 separate episodes during the third postprandial hour.¹

3. Sleep GER is indicated by an esophageal pH less than 4.0 during greater than 4 minutes while asleep, beyond the 2-hour postprandial period.¹¹

Pulse Oximetry.—Continuous arterial oxygen saturation (Sao₂) was measured using a Nellcor N-100 pulse oximeter (Nellcor Inc, Hayward, Calif) with the oxygen sensor attached to the right great toe.^{15,16} Sao₂ data were recorded and temporally synchronized with the esophageal pH monitoring device. To exclude technical artifacts inherent in pulse oximetry, only episodes of Sao₂ less than 90% that persisted for greater than 3 minutes were considered significant.

Transthoracic Impedance Pneumocardiography.—Impedance pneumocardiography was performed employing a Healthdyne/Trend event recorder (Healthdyne Inc, Marietta, Ga). Abnormal tracings were defined as follows: (1) apnea (absence of chest wall movement) for greater than 15 seconds and (2) bradycardia and/or periodic breathing exceeding age-related norms.¹⁷⁻¹⁹ During

the study period, detailed infant activities (feeding, ALTE symptoms, and awake and sleep periods) were recorded in individual patient diaries. These observations were correlated with monitoring data as described above. Results were hand scored separately by an investigator unfamiliar with the patient, and diaries and recordings were not identified with patients' names. Audible alarm systems were not employed. All infants were studied after obtaining informed parental consent and this protocol was approved by the Committee for the Protection of Human Subjects (Institutional Review Board), New York Medical College.

Statistical Analysis

χ^2 Analysis and Student's *t* test for unpaired data were used to compare monitoring results between infants with ALTE and control subjects. Data correlating relationships between esophageal acidification and desaturation were analyzed using linear regression and one-way analysis of variance.

RESULTS

Pneumograms did not reveal apnea, bradycardia, or periodic breathing. Data collected from pH and oximetry monitoring in both patients with ALTE and control groups are summarized in Table 2. In infants with ALTE, despite the absence of a clinical vomiting history

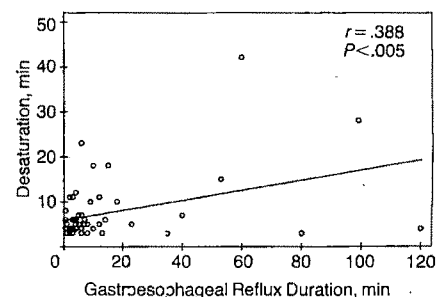


Fig 1.—Correlation between length of individual reflux episodes and associated oxygen desaturation events.

in all but 2 patients (Table 1), a total of 491 GER episodes were monitored in 15 of 16 infants (mean number of episodes, 28.8 per patient), compared with 159 episodes documented in 6 of 6 control subjects (mean number of episodes, 26.5 per patient). However, dramatic differences in the incidence of hypoxemic events between groups was noted.

Prolonged, ie, greater than 3 minutes, Sao₂ reductions were observed in none of the control subjects. Conversely, a total of 60 episodes of desaturation were monitored in infants with ALTE (P < .01), and 54 of 60 of these episodes commenced during a period of esophageal desaturation (pH < 4.0). Temporal correlation between esophageal pH and pulse oximetry recordings demonstrates that onset of significant reflux-associated hypoxemia occurred within 3.9 \pm 0.4 minutes (mean \pm SD) following a decrease in esophageal pH to less than 4.0, with a mean duration of 7.3 \pm 0.5 minutes for each desaturation event.

As shown in Fig 1, linear regression analysis of combined pH and oximetry data indicates a significant correlation (P < .05) between the duration of individual periods of esophageal acidification and associated hypoxic episodes. Results of monitoring demonstrate that Sao₂ reductions occurred during feeding, during the immediate postprandial period, and during sleep (Fig 2). There were no episodes of awake, delayed postprandial GER associated with hypoxemia. Similar to our earlier reported data,⁹ while the overall incidence of GER (determined according to the above described criteria) was similar in both patient groups, infants with ALTE had a markedly increased incidence of GER during sleep (Fig 2) when compared with control subjects (77% vs

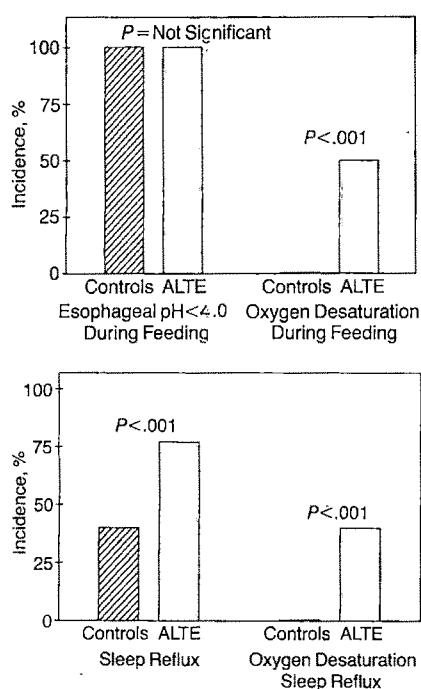


Fig 2.—Top, Incidence of esophageal acidification and oxygen desaturation during feeding. Bottom, Incidence of esophageal acidification and oxygen desaturation during sleep. ALTE indicates apparent life-threatening event(s).

40%, respectively; $P < .001$). Throughout the monitoring period, infants with ALTE manifested an overall 93% incidence of significant hypoxemia associated with reflux (0% in control subjects, $P < .001$), and sleep reflux-related SaO_2 reduction occurred in 40% of patients with ALTE (0% in control subjects, $P < .001$).

To assess the contribution of esophageal acidification per se to the development of hypoxemia, apple juice feedings (pH 3.5, see "Methods" section) were given to both infants with ALTE and control subjects, and a lower esophageal pH of less than 4.0 was achieved in all patients. However, while control sub-

jects demonstrated a 0% incidence of hypoxemia during oral apple juice feedings, 50% of infants with ALTE demonstrated significant acid-induced SaO_2 decreases (Fig 2).

COMMENT

These data demonstrate that clinically inapparent, but significant, oxygen desaturation (in the presence of chest wall movement) occurring during both awake and sleep periods is temporally associated with GER in a group of infants presenting with ALTE. Conversely, in control subjects manifesting vomiting/regurgitation without evidence of cardiorespiratory compromise, GER does not result in significant SaO_2 reduction. Intraesophageal pH monitoring results also confirm our previous observations suggesting that GER occurs in a high percentage of patients with ALTE, despite absence of a clinical history of vomiting.⁹ Finally, linear regression analysis demonstrates a significant correlation between the duration of individual GER episodes and associated hypoxemic events.

Experimental evidence supports an association between GER and alterations in cardiopulmonary function. In newborn piglets, Kenigsberg et al²⁰ observed reflex bradycardia occurring following reduction of esophageal pH to less than 3.5. Using a feline model, Tuchman and colleagues²¹ demonstrated that microaspiration into the trachea is a more likely mechanism for bronchospasm associated with GER than simple acid reflux into the esophagus.

Previous clinical studies indicate a causal relationship between esophageal acidification and the onset of obstructive apnea.^{2,3,22-25} For example, an increased incidence of GER was noted in infants with a history of apnea, and res-

piratory compromise has been reported in infants following regurgitation episodes.^{22,23} Using simultaneous esophageal pH, nasal airflow, and impedance pneumocardiographic monitoring, observations by Herbst et al² and Spitzer and colleagues¹ indicate a direct relationship between GER and the onset of obstructive apnea (ie, reduced nasal air flow in the presence of chest wall movement). In contrast to these data, other investigators have failed to demonstrate a GER/hypoxia association.²⁶ However, failure to assure gastric acidification with the use of apple juice or 5% dextrose in water feedings¹⁹ may account for these monitoring differences.

Although our results indicate an association between the presence of esophageal acid and the incidence of relative oxygen desaturation, none of the infants studied developed symptoms of ALTE during the 16- to 20-hour monitoring period.

Therefore, a conclusive cause-and-effect relationship between GER and the development of apneic syndromes remains to be established. Additional monitoring data, including follow-up studies of these infants during and after long-term medical management for GER, should clarify this issue. Nevertheless, evidence demonstrating that the severity of GER-induced hypoxemia may be related to the duration of esophageal acidification is intriguing and warrants further investigation.

Finally, monitoring data suggesting a direct relationship between the presence of esophageal acid and a reduction in oxygen saturation (SaO_2) in infants with ALTE support the use of prolonged intraesophageal pH studies in patients presenting with an ALTE.

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ARCHIVES OF DERMATOLOGY

Prior X-ray Therapy for Acne Related to Tumors of the Parotid Gland

Susan Preston-Martin, PhD (*Arch Dermatol*. 1989;125:921-924)

Epidermolysis Bullosa Acquisita in Childhood: Differentiation From Hereditary Epidermolysis Bullosa

Catherine C. McCuaig, MD, FRCPC; Lawrence S. Chan, MD; David T. Woodley, MD; James E. Rasmussen, MD; Kevin D. Cooper, MD (*Arch Dermatol*. 1989;125:944-949)

The Importance of Parents' Concerns About Their Child's Development

Frances P. Glascoe, PhD; William A. Altemeier, MD; William E. MacLean, PhD

• Parents are often concerned about their child's development, but it is unknown whether concerns indicate actual developmental problems. Pilot studies within 96 families showed that parents' concerns about their children's development took the form of value judgments, could be classified into commonly accepted developmental domains, and related to performance on screening tests. In our study, 100 families seeking pediatric care were asked to list any concerns about their child's development while their children received developmental screening. Eighty percent of the children who failed screening had parents with concerns about articulation, language, fine-motor skills, or global development. Ninety-four percent of the children who passed screening had parents with no concerns or concerns in other developmental areas. The types of concerns parents raised did not vary significantly with level of education, experience in child rearing, or other demographic variables. These results suggest that parental concerns may be a helpful adjunct to standardized developmental screening.

(AJDC. 1989;143:955-958)

Parents seeking care from their child's pediatrician often have concerns about development and other psychosocial issues. In 1983, Hickson et al¹ showed that 70% of parents in pediatric waiting rooms were less worried about medical issues than about discipline, behavior, personality, and social development. Despite this prevalence, the pres-

ence of psychosocial concerns does not often lead to active intervention by pediatricians for two reasons. First, parents often fail to raise psychosocial concerns. Hickson et al¹ found that only 28% of parents indicated that they had discussed or planned to present their most important nonmedical concern to the pediatrician. Second, pediatricians may be reluctant to respond to psychosocial concerns² perhaps because of limitations in reimbursement, time, training, or interest.

The importance of parents' concerns about their child's development is unknown. Does a developmental concern reflect a child's true deviation or does it simply express parental anxiety? In our study, we systematically elicited parental concerns about child development to assess their importance. The purpose was to (1) identify the range of concerns parents have about their child's development, (2) evaluate the relationship between parents' concerns and their child's developmental status, and (3) consider how parents derive their concerns. The results may guide pediatricians in responding to parental concerns about development.

SUBJECTS AND METHODS

The first of two pilot studies helped sample and classify parental concerns. Fifty parents, randomly selected in equal numbers from general pediatric and developmental clinics, were asked, "Please tell me any concerns you have about the way your child is learning and developing." Categories of responses were extrapolated by searching for contrasts and similarities across and within responses.^{3,4} The Table presents representative answers in the 12 categories, 10 of which addressed the commonly accepted developmental domains.

The second pilot study determined whether the concerns of a second group of parents fit into the above 12 categories and whether concerns could be grouped into two types—

those more likely and those less likely to reflect actual developmental problems. Subjects included 46 parent-child dyads drawn equally from the same sites. Parents were asked the same experimental question, and children received developmental screening using a variety of standardized measurements.

No additional categories of concerns were needed. Reliability of categorization was assessed by having two researchers independently code responses on 20% of the cases. There was 80% to 100% agreement, with a mean of 95% agreement for each of the 12 categories. Children who passed screening tended to have parents with either no concerns or concerns about their children's behavior control, social-affective skills, personal-adaptive skills, medical-sensory status, gross-motor skills, or school skills. These responses were labeled group A. Children who failed screening tended to have parents with concerns about their children's articulation, expressive language, receptive language, fine-motor skills, or global development. These responses were labeled group B.

Subjects and Sites

Subjects included 108 parent-child dyads seeking outpatient pediatric care in either a private children's hospital or a city-supported hospital. Subject selection was made according to the availability of families. Parents of children who were not acutely ill or older than 6 years were asked to participate. Eight subjects declined to participate in the study and 100 gave informed consent. The 100 parents were mainly from urban or suburban settings (85%), mothers (85%), married (58%), and had an education level of 12th grade or more (71%). The children were typically white (54%), male (56%), firstborn (54%), siblings (66%), and averaged 37 months of age (range, 2 weeks to 71 months; SD, 20.5 months).

Measurement

Parents were asked the following questions: (1) "What concerns do you have about your child's learning and development?" (2) "How do you know what a child (the same age as your child) should be doing? What kinds of

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Categories of Parental Concerns About Children's Development	
Category	Typical Responses
No concerns	Development is normal; typical child; coming along just fine
Behavior control	Stubborn; overly active; short attention span; spoiled; aggravating; throws fits; only does what she wants
Social-affective skills	Wants to be left alone; mood swings; clingy; whiney; bothered by changes; angry; disinterested in usual things; easily led; easily frustrated; immature
Personal-adaptive skills	Won't do things for himself; won't tell me when she is wet; not toilet trained yet; still wants a bottle
Medical-sensory status	Ear infections; asthma; small for age; sick a lot
Gross-motor skills	Clumsy; walks funny; can't ride a bike yet; falls a lot; limps; poor balance
School skills	Can't write his name (scored also with fine motor); doesn't know colors or numbers; just not learning to read; can't remember letter sounds; knows stuff one day but not the next
Articulation	Not making speech sounds correctly; hard to understand; stutters; sounds funny when he talks
Expressive language	Not talking like he should; uses short sentences; can't always say what she means; doesn't always make sense
Receptive language	Doesn't understand what we say to him; doesn't listen well
Fine-motor skills	Can't stay in the lines when he colors; can't write name; can't draw shapes; can't hold a pencil correctly; can't get food to mouth with a spoon yet
Global development	Seems behind; learns slowly; problems with learning; late to learn to do things; slow learner; learns but takes his time

information do you use to figure out how he or she is developing?" (3) "Has anyone ever had concerns about his or her development, such as a physician, teacher, friend, or relative?" (4) "Has his or her development ever been tested?" Parents were also asked to provide demographic and other parent-child data, ie, numbers of children in the family, child's birth order, child's participation in day-care, parents' exposure to handicapped relatives, parents' level of education, area of residence, hours per weekday spent with the child, and perceptions about children's medical problems rated as very serious, somewhat serious, or not very serious.

Children's development was assessed with the screening subtest of the Developmental Profile-II (DP-II),⁵ which was standardized in 1982 on a nationally stratified sample of 3008 children. Subtest items assess the better predictors of subsequent school performance—cognitive, expressive, and receptive language and fine-motor and preacademic or academic skills.^{6,7} Scores correlate highly with individually administered measurements of intelligence, and quotients of 70 or less are considered failing.^{5,8} Parent reporting, direct testing, or both can be used, and measurement decisions were left to the examiner, who had a PhD in child development. Because the DP-II does not screen for articulation impairments, the single most common handicapping condition,⁹ when parents raised concerns about speech, children were also administered the Articulation Screening Test¹⁰ as were an equal number of children whose parents were not concerned about articulation. Children who failed either test were scored as failing. The experimental interview and developmental mea-

surement(s) were administered by the same examiner, with the order of administration alternated to minimize examiner bias and measurement effects.

RESULTS

The Relationship Between Parents' Concerns and Screening Test Results

Seventy-nine of the 100 parents gave group A responses. Fifty-five parents had no concern about development, and 24 had concerns about behavior control (4% of 100), personal-adaptive skills (2%), social-affective skills (4%), gross-motor skills (6%), medical-sensory status (2%), or school skills (4%). Eighty of the 100 children passed developmental screening. Of their 80 parents, 55 had no concerns and 20 had concerns about behavior control, personal-adaptive skills, social-affective skills, gross-motor skills, medical-sensory status, or school skills. Thus, 75 (94%) of the 80 parents whose children passed screening had group A responses.

Twenty-one of the 100 parents gave group B responses, including concerns about articulation (9% of 100), expressive language (8%), receptive language (1%), fine-motor skills (2%), or global development (6%). Twenty of the 100 children failed one or both screening tests, a failure rate that exceeds the 12% prevalence of handicapping conditions⁹ and may be caused by the preponderance of subjects at risk for later de-

velopmental problems from preterm birth or lower socioeconomic background. Thus, 16 (80%) of the 20 parents whose children failed screening had group B responses.

Group A and B responses were significantly correlated with screening test performance ($\phi = .72$, $P < .001$).¹¹ Parents whose children failed screening also had a greater number of concerns (mean = 2.05) than had parents whose children passed screening (mean = .36). A *t* test showed these differences were significant ($t[98] = 9.14$, $P < .001$).

How Parents Derive Their Concerns

Most parents (96 of 100) indicated at least one source of information for figuring out how their child was developing (mean = 3.1; range, 0 to 8). Most parents (59% of 96) compared their child with others (eg, "He's up there with the rest of the kids." Or "She can't do what other kids can do."). In terms of development, 43% of the parents thought their children compared favorably with others, while 11% made unfavorable comparisons, and 5% made both types of comparisons. Favorable comparisons correlated slightly with group A responses ($\phi = .17$, $P < .05$) and nonsignificantly with passing screening tests ($\phi = .13$). Unfavorable comparisons correlated significantly with group B responses ($\phi = .40$, $P < .001$) and with failing scores on developmental screening tests ($\phi = .51$, $P < .001$). Other sources of information included talking with medical professionals (40%), reading child-care literature (40%), and knowledge of development gained from previous observation or experience with children (53%).

Twenty-three of the 100 parents reported some prior exposure to the opinions of others—16 mentioned the concerns of physicians, teachers, friends, or relatives, 1 mentioned that her child had had previous developmental testing, and 6 mentioned both. Of the 23 parents, 13 had group B responses and children who failed screening, 6 had group A responses and children who passed, and 4 had responses that did not relate to the screening test results. Thus, prior developmental testing, the opinions of others, or both correlated significantly with the two types of parental responses ($\phi = .59$, $P < .001$).

and with screening test performance ($\phi = .62, P < .001$).

The Relationship of Demographic and Other Parent-Child Characteristics to Parents' Concerns and Screening Results

There were no demographic differences or other differences in parents who gave group A responses vs group B responses or in children who passed vs those who failed screening tests based on the numbers of children in the family; child's birth order; participation in day-care; parents' exposure to handicapped relatives, level of education, area of residence, hours per weekday spent with the child, perceptions of the seriousness of children's medical problems; and whether the interview or screening tests were conducted first. Children's ages correlated significantly with the screening test performance and type of parental response. Older children were more likely to fail screening ($\phi = .40, P < .001$) and to have parents with group B responses ($\phi = .30, P < .001$). The mean ages of children passing and failing screening were 30 months ($SD = 20.1$ months) and 50 months ($SD = 13.3$ months).

Demographic and other characteristics did not seem to influence whether parental responses corresponded to screening test performance. The 91 parents whose responses related to screening results (ie, group A responses and passing screening or group B responses and failing screening) did not have significantly different demographic or other characteristics from the 9 whose responses did not relate to the results.

COMMENT

The use of information from parents in screening development is not new. Standardized tests such as the Denver Developmental Screening Test-Revised and the Minnesota Child Development Inventory use parental report of skills such as dressing and communicating. Similarly, pediatricians often request a history of selected developmental milestones in developmental screening.^{6,7} In fact, it is difficult to find any type of developmental measurement for young children that does not make some use of parental information. Nevertheless, all available tests use pa-

rental report of specific behaviors, and parents play no role in appraising development; this task is left to professionals.

Little is known about the ability of parents to appraise their child's development. However, most parents cannot identify the typical ages at which children achieve various milestones.¹²⁻¹⁷ Since their knowledge of development is limited, it seems unlikely that parents would have skills in appraisal. Nevertheless, the prevalence of parental concerns about development suggests that they think about the subject¹ and may try to determine on their own whether their child's development is appropriate.

In this study, parents were asked to state any concerns about the way their child was learning and developing, and they responded with a range of concerns that could be categorized into commonly recognized developmental domains. Concerns were given in response to an open-ended question rather than to queries about specific skills or behaviors. Parents' answers, although often short and simple, took the form of value judgments. It was unclear to what degree such appraisals were the result of a prior, continuous parental assessment as opposed to opinions first formed in response to the interview, but the frequent mention of comparisons by parents as a method for deriving concerns suggests that the former is more likely.

Concerns about development were common and were expressed by 45% of all parents. While this figure seems high, the range of concerns was broad, with some appearing much less likely to reflect true developmental problems than others. This assumption was supported by a pilot study that indicated that certain groups of concerns were related to failing screening tests while others were not. The absence of concerns or concerns about behavior control, personal-adaptive skills, social-affective skills, gross-motor skills, medical-sensory status, or school skills—identified as group A responses—corresponded with passing screening tests. Concerns about articulation, expressive language, receptive language, or global development—identified as group B responses—were associated with failing screening tests. Although the separation of A and B con-

cerns was made on an experimental basis, it does not deviate substantially from current concepts about the relative importance of developmental domains with the exception of school skills.^{7,18} For example, gross-motor skills concerns were more appropriate for inclusion in group A responses since they are only a weak predictor of overall developmental status.^{6,7} As further evidence that the grouping of concerns was legitimate, parents with group B concerns tended to indicate by comparisons that their children were having actual developmental difficulties, while parents with group A concerns did not. The lack of significance in the demographic or child-rearing variables suggests that parents of differing backgrounds are equally able to assess their child's development, a finding supported by previous research.^{19,20}

How is it that parents' concerns seemed closely related to the developmental status of children, especially when most studies find parents ill-informed about child development?¹²⁻¹⁷ As expected, they did not rely primarily on formal knowledge of development in appraising their children. Instead, the most common method for analyzing development was comparing one's own children with the children of others. The conclusions parents reached through comparisons were highly correlated with types of concerns (A and B responses) and with screening test performance. This suggests that comparisons were an important part of determining concerns about development and their accuracy. Some of the agreement between screening tests and parents' concerns may also be explained by parental exposure to the opinions of others or to previous developmental testing. However, only 23% of parents reported exposure, and parents may have introduced concerns to professionals.

Our study shows a strong relationship between certain types of parental concerns and child development, and although pediatricians should listen to these concerns, we do not recommend relying in any way on concerns as an alternative to standardized developmental screening measures. Nor should pediatricians ignore concerns that currently seem unrelated to screening test performance. Rather, parental con-

cerns about development should be viewed as a helpful adjunct to routine developmental screening and a means for focusing the content of parent-physician communication. Additional research is needed to confirm and extend these findings, including cross-validation with a larger and more stratified population that includes subjects from private pediatric clinics; improvement in research design such that separate examiners "blinded" to each other's data assess parental concerns and development; use of diagnostic developmental tests rather than screening measurements to determine developmental

status; formal, multitrait-multimethod assessment of all developmental areas to determine the exact relationship between the content of parents' concerns and performance in each developmental domain; and a determination of variables influencing the relationship between concerns and screening results (eg, "vulnerable child" syndrome might lead to unwarranted concern, while the perception that a handicapped child is receiving optimal intervention might reduce concerns about delayed development).

Lichtenstein and Ireton,²¹ leaders in developmental screening, suggest that

one of the challenges in working with parents is "how to obtain the precious information they possess in a manner that is not only valid and cost-effective but also instrumental in the process of building positive, working relationships." This article suggests that when parents are concerned about their child's development, health care professionals should pay attention. If our findings are confirmed and extended, the practice of routinely eliciting parental concerns about development might be supported as a simple, brief approach to prescreening child development.

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In Other AMA Journals

ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

Interpretation of Elevated Postmortem Serum Concentrations of Digoxin in Infants and Children

Gideon Koren, MD; Dawn Beatie; Stephen Soldin, PhD; Thomas R. Einerson, PhD; Stuart MacLeod, MD, PhD (*Arch Pathol Lab Med*. 1989;113:758-761)

Intracerebral Hemorrhage Associated With Cocaine Abuse

Kurt B. Nolte, MD, Benjamin B. Gelman, PhD, MD (*Arch Pathol Lab Med*. 1989;113:812-813)

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Radiological Case of the Month

Kenneth R. Katz, MD, Robert W. Emmens, MD (*Contributors*);
Beverly P. Wood, MD (*Contributor and Section Editor*)

A 4-year-old black boy was referred to the emergency department for evaluation of acute dehydration. He had been in good health until 6 months earlier, when he began to eat smaller portions of food and was noted to spit food out and hide it in the furniture. He tolerated liquids well, but often became teary-eyed while attempting to eat. There was a recent history of progressive drooling and nasal congestion. On admission he was afebrile and had diminished skin turgor. His weight was below the third percentile, although he had been in the 40th percentile 9 months earlier. A urinalysis showed specific gravity of 1.032 and trace ketones. The serum electrolyte level was in the normal range. His hematocrit was 0.36, and the white blood cell count was $11.4 \times 10^9/L$, with a differential cell count of 0.29 segmented neutrophils, 0.03 band cells, and 0.53 lymphocytes. The results of a tine test were negative.

An esophagogram was obtained.

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Contributed from the Departments of Pediatrics (Dr Katz), Pediatric Surgery (Dr Emmens), and Radiology (Dr Wood), University of Rochester (NY) Medical Center.

Reprint requests to Department of Radiology, University of Rochester Medical Center, PO Box 648, 601 Elmwood Ave, Rochester, NY 14642 (Dr Wood).

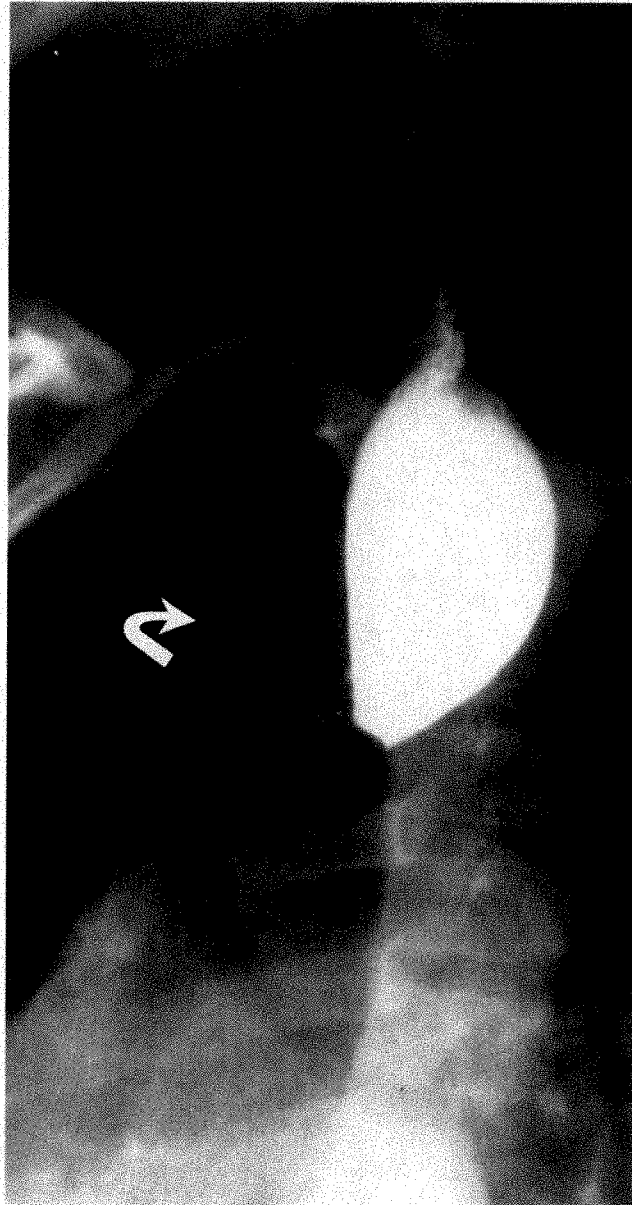


Figure 1.

Esophageal Obstruction and Abscess Formation Secondary to Impacted, Eroding Tiddlywink

Fig 1.—The esophagogram shows an obstruction to passage of barium past the upper thoracic esophagus. Note an extrinsic mass impression narrowing the adjacent trachea (arrow) and an ovoid lucency within the mass.

Fig 2.—The computed tomographic scan shows tracheal displacement (curved arrow) and swallowed contrast filling the mediastinal mass (straight arrow). Note the disc lucency in the mass immediately anterior to the vertebra.

Fig 3.—Sagittal midline magnetic resonance image shows dilated esophagus (solid arrow) and high-signal mass containing disklike low-signal foreign body (open arrow).

The operative exploration of the esophagus revealed a 2-cm-diameter blue, plastic tiddlywink (disk). The object had eroded the upper esophagus and was embedded in granulation tissue adjacent to the lumen. The lumen was obscured by the mass and friable, edematous mucosa. Two weeks following surgery, the patient was discharged, has done well, and has regained his lost weight.

Swallowed foreign bodies are common in children between the ages of 1 and 4 years. The objects most commonly seen in the United States are parts of toys and disks (eg, coins or buttons). Impaction of swallowed objects is rare in children.¹ However, the site of impaction is at the cricopharyngeus in the cervical esophagus or in the upper thoracic esophagus.^{1,2} Although adults with impacted foreign

bodies frequently demonstrate underlying disease, children with impaction are usually normal.²

The impacted foreign body may erode the esophagus by pressure or perforate it if it is sharp. Symptoms from impacted foreign bodies can be subtle. Those noted include wheezing, refusal to eat, increased salivation, pain on swallowing, vomiting, and altered consciousness.³⁻⁶

Examination, including a chest roentgenogram and a contrast esophagogram, usually indicates the diagnosis, especially in the case of a radiopaque foreign body. In our case, the plastic object was mistaken for air within an abscess or mass obstructing the esophagus. Further examination with computed tomography (Fig 2) and magnetic resonance imaging (Fig 3) followed. Plastic demonstrates the

same characteristics as gas on radiography, computed tomography, and magnetic resonance imaging.

We should suspect that a young child with symptoms of esophageal obstruction may have an impacted foreign body, even when it is not easily visible radiographically.

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Figure 2.

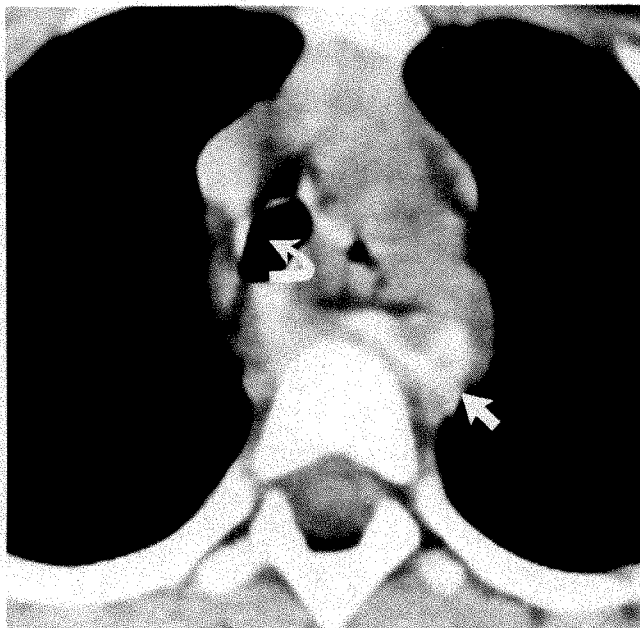
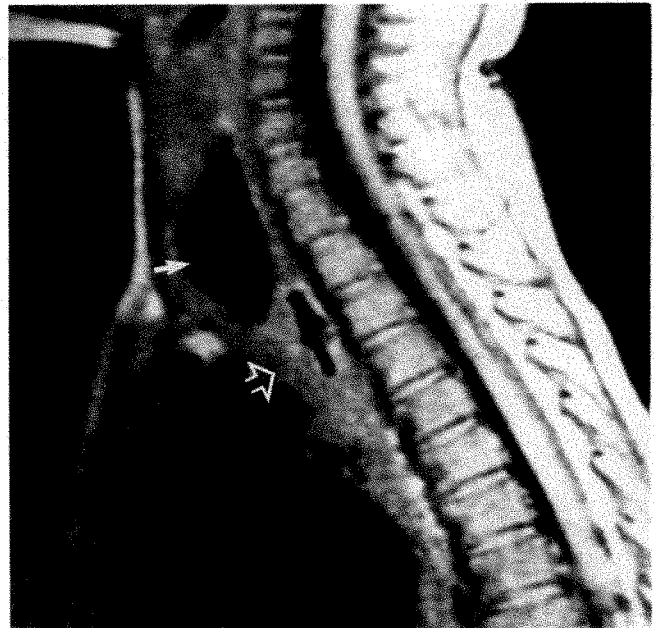


Figure 3.



Picture of the Month

Abner H. Levkoff, MD, John C. Maize (*Contributors*);
Murray Feingold, MD (*Section Editor*)



Figure 1.



Figure 2.



Figure 3.

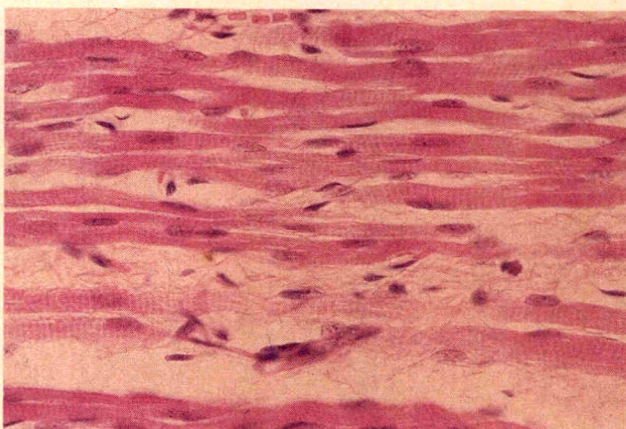


Figure 4.

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Contributed from the Department of Pediatrics,
Medical University of South Carolina,
Charleston.
Reprint requests to National Birth Defects
Center, Franciscan Children's Hospital, 30 War-
ren St, Brighton, MA 02135 (Dr Feingold).

Denouement and Discussion

Fig 1.—Full facial view of hamartoma.

Fig 2.—Left lateral view of hamartoma.

Fig 3.—Close-up of the midface showing hamartoma.

Fig 4.—Striated muscle bundles (hematoxylin-eosin, original magnification $\times 400$).

Congenital rhabdomyomatous mesenchymal hamartoma of the skin, to our knowledge, has been described once previously as a single pedunculated appendage on the chin of a newborn. In that case, the appendage had an abnormal arrangement of dermal mesenchymal elements, with a prominence of skeletal muscle. In the patient shown herein, the connective-tissue core of the pulp contained adipose cells and striated muscle bundles that were oriented primarily parallel to the long axis. The epidermis was slightly hyperplastic and under higher magnification demonstrated striated

muscle bundles. Pathologically, it was characterized as a hamartoma because of the abnormal mixture of normal cells (ie, striated muscle, mesenchyme, and skin) in an appropriate area, the face muscles of expression.

Other than a very unusual appearance, the striking feature was the random contractile movements of the appendages, giving a snakelike appearance. Computed tomographic scan revealed no involvement of underlying bone. A bilateral leukokoria due to sclerocornea was also present, with no retinal detachment detected by computed tomographic scan. Pri-

mary surgical revision resulted in dramatic improvement of the patient's appearance.

This condition, at present, is not known to be associated with anomalies of other organ systems, nor has any inheritance pattern been established. The lesions are not similar to fetal rhabdomyomas or connective-tissue nevi.

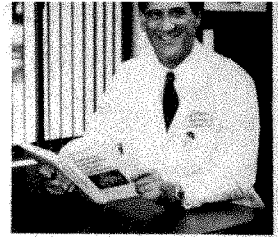
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The Editors welcome contributions to PICTURE OF THE MONTH and RADIOLOGICAL CASE OF THE MONTH. Those who wish to contribute should send their manuscripts to Dr Feingold (Picture of the Month), National Birth Defects Center, Franciscan Children's Hospital, 30 Warren St, Brighton, MA 02135, or Dr Wood (Radiological Case of the Month), University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.

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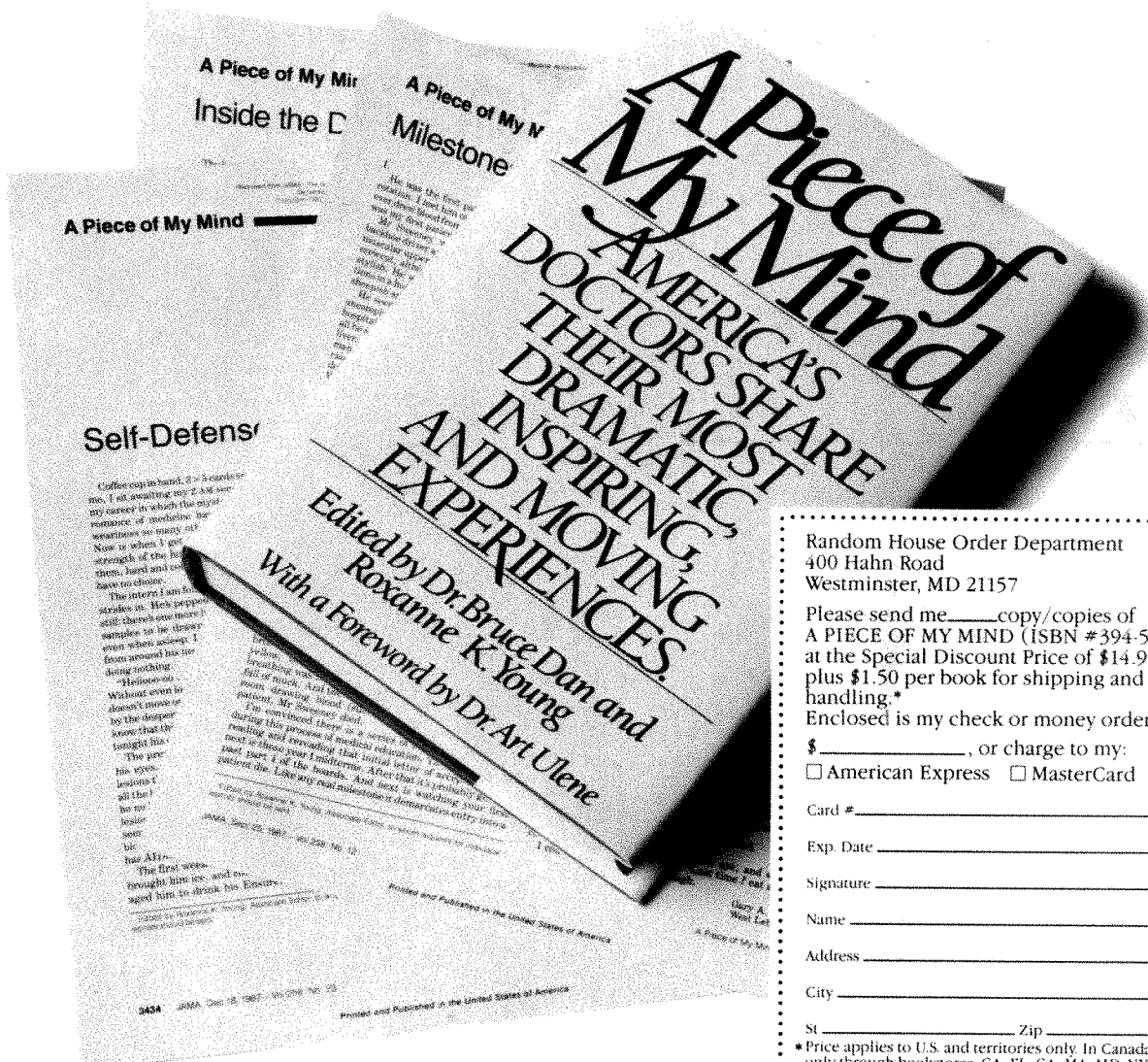
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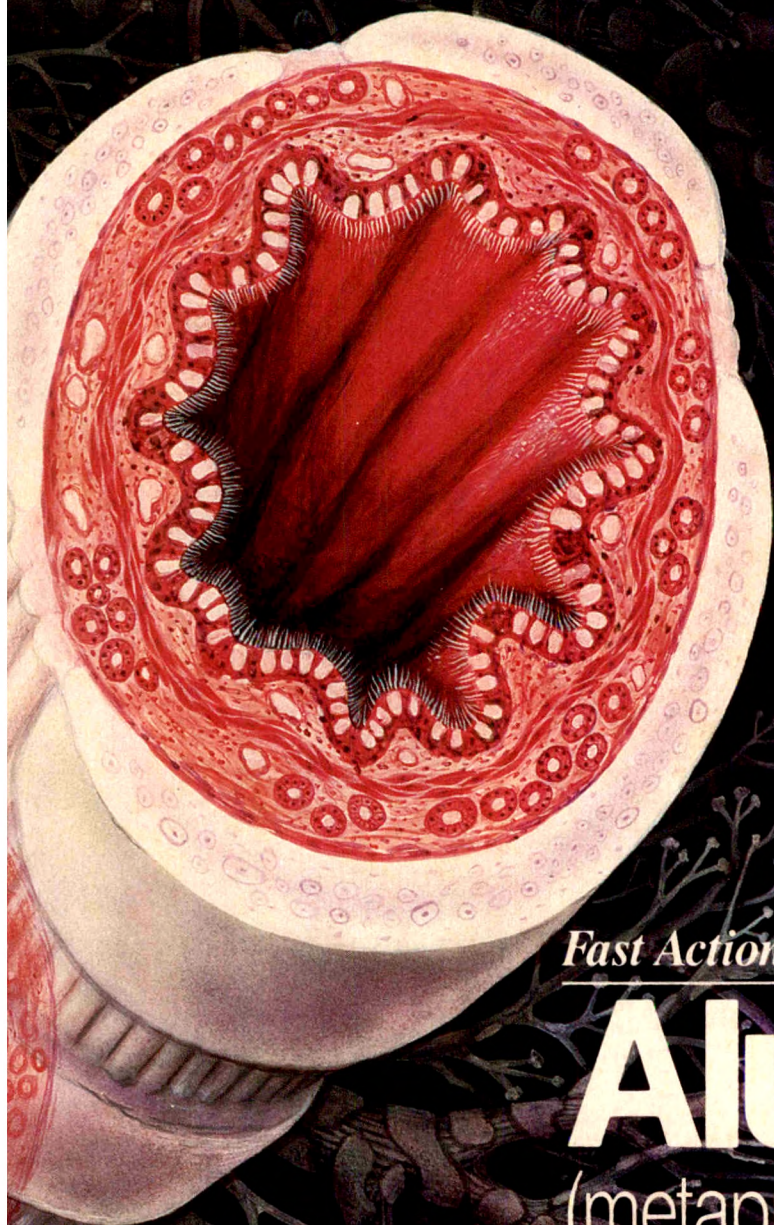
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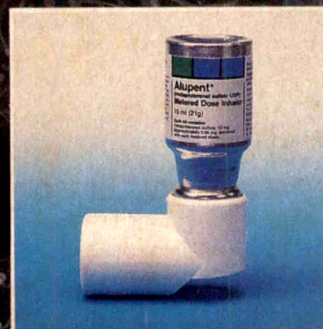
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Fast Action, Fast Relief in Asthma

Alupent[®]

(metaproterenol sulfate)
Inhalation Aerosol

15 ml; 15 mg/ml (each metered dose delivers 0.65 mg metaproterenol sulfate)

*In controlled single-dose studies with Alupent Inhalation Aerosol, the duration of effect of two to three inhalations (20% or greater increase in FEV₁) has varied from one to five hours. In multiple-dose studies (up to q.i.d.), the duration of effect for a similar dose of Alupent has ranged from about one to two and a half hours.

Please see following page for brief summary of prescribing information

Fast Action, Fast Relief in Asthma

Alupent®

(metaproterenol sulfate)

Tablets	Inhalation Aerosol	Syrup	Inhalation Solution	Inhalation Solution
10 and 20 mg	15 ml†	10 mg/5 ml	5% 10 ml and 30 ml	Unit-dose Vials 0.4% and 0.6%

†15 mg/ml (each metered dose delivers 0.65 mg metaproterenol sulfate)

Brief Summary of Prescribing Information

CONTRAINDICATIONS Use in patients with cardiac arrhythmias associated with tachycardia is contraindicated.

Although rare, immediate hypersensitivity reactions can occur. Therefore Alupent® (metaproterenol sulfate USP) is contraindicated in patients with a history of hypersensitivity to any of its components.

WARNINGS Excessive use of adrenergic aerosols is potentially dangerous. Fatalities have been reported following excessive use of Alupent® (metaproterenol sulfate USP) as with other sympathomimetic inhalation preparations, and the exact cause is unknown. Cardiac arrest was noted in several cases. Paradoxical bronchoconstriction with repeated excessive administration has been reported with sympathomimetic agents. Therefore, it is possible that this phenomenon could occur with Alupent. Patients should be advised to contact their physician in the event that they do not respond to their usual dose of a sympathomimetic amine aerosol.

PRECAUTIONS Because Alupent® (metaproterenol sulfate USP) is a sympathomimetic drug, it should be used with great caution in patients with hypertension, coronary artery disease, congestive heart failure, hyperthyroidism or diabetes, or when there is sensitivity to sympathomimetic amines.

Information for Patients Extreme care must be exercised with respect to the administration of additional sympathomimetic agents. A sufficient interval of time should elapse prior to administration of another sympathomimetic agent.

Carcinogenesis Long-term studies in mice and rats to evaluate the oral carcinogenic potential of metaproterenol sulfate have not been completed. Studies of metaproterenol sulfate have not been conducted to determine mutagenic potential or effect on fertility.

Pregnancy *Teratogenic Effects: Pregnancy Category C.* Alupent has been shown to be teratogenic and embryocidal in rabbits when given orally in doses 620 times the human inhalation dose and 62 times the human oral dose. There are no adequate and well-controlled studies in pregnant women. Alupent should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Oral reproduction studies in mice, rats and rabbits showed no teratogenic or embryocidal effects at 50 mg/kg, corresponding to 310 times the human inhalation dose and 31 times the human oral dose. Teratogenic effects in the rabbit included skeletal abnormalities and hydrocephalus with bone separation.

Nursing Mothers It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Alupent is administered to a nursing woman.

Pediatric Use Consult package insert for age limit.

ADVERSE REACTIONS Adverse reactions are similar to those noted with other sympathomimetic agents. Adverse reactions such as tachycardia, hypertension, palpitations, nervousness, tremor, nausea and vomiting have been reported.

The most frequent adverse reactions to Alupent® (metaproterenol sulfate USP) Inhalation Solution are nervousness and tachycardia which occur in about 1 in 7 patients, tremor which occurs in about 1 in 20 patients and nausea which occurs in about 1 in 50 patients. Less frequent adverse reactions are hypertension, palpitations, vomiting and bad taste which occur in approximately 1 in 300 patients.

HOW SUPPLIED *Inhalation Aerosol:* Each canister of Alupent® (metaproterenol sulfate USP) Inhalation Aerosol contains 225 mg of metaproterenol sulfate as a micronized powder in inert propellants. Alupent Inhalation Aerosol with mouthpiece (15 ml). Alupent Inhalation Aerosol refill (15 ml). Store below 77°F (25°C). Avoid excessive humidity.

Inhalation Solution: Alupent Inhalation Solution is supplied as a 5% solution in bottles of 10 ml or 30 ml with accompanying calibrated dropper.

Store below 77°F (25°C). Protect from light. Do not use the solution if it is brown or has a precipitate. Alupent Inhalation Solution Unit-dose Vial is supplied as a 0.4% or 0.6% clear colorless or nearly colorless solution containing 2.5 ml with 25 vials per box. Store below 77°F (25°C). Protect from light. Do not use the solution if it is brown or has a precipitate.

Syrup: Alupent is available as a cherry-flavored syrup, 10 mg per teaspoonful (5 ml), in 16 fl. oz. bottles. Store below 86°F (30°C). Protect from light.

Tablets: Alupent is supplied in two dosage strengths as scored, round white tablets in bottles of 100. Tablets of 10 mg coded BI/74. Tablets of 20 mg coded BI/72.

Storage for bottles. Store below 86°F (30°C). Protect from light.

Storage for blister samples. Store below 77°F (25°C). Protect from light.

Consult package insert before prescribing.

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Effect of Pancreatic Enzyme Supplements on Iron Absorption

William T. Zempsky, MD; Beryl J. Rosenstein, MD; John A. Carroll, MD; Frank A. Oski, MD

• Iron deficiency has been reported in one third of patients with cystic fibrosis. There are data that suggest that iron absorption is increased with exocrine pancreatic deficiency and that administration of pancreatic enzymes may impair oral iron absorption. We compared oral iron absorption over a 3-hour period in the presence and absence of exogenous pancreatic enzymes in 13 stable young-adult patients with cystic fibrosis and 9 age-matched control patients. Although none of the patients with cystic fibrosis had a hemoglobin level less than 119 g/L, serum ferritin levels were less than 25 µg/L in 5 of the 13 patients, and the mean corpuscular volume was significantly lower in the patient group (86.1 ± 2.7 vs 90.9 ± 5 fL). Baseline mean serum iron levels were higher in controls (18.9 ± 5.9 µmol/L) than in patients (11.9 ± 6.3 µmol/L). There was no difference in iron absorption in the absence of exogenous pancreatic enzymes. Significant impairment of iron absorption was detected in both patients with cystic fibrosis and controls after administration of a preparation of pancreatic enzymes. There was an inverse relationship between iron stores, as measured by serum ferritin, and iron absorption. These findings suggest that long-term consumption of pancreatic enzymes by patients with cystic fibrosis may contribute to iron deficiency.

(AJDC. 1989;143:969-972)

Iron deficiency has been reported in 33% to 66% of patients with cystic fibrosis (CF).¹⁻³ The etiology is probably multifactorial, including inadequate dietary intake, blood loss, iron malabsorption, and chronic infection. There have been both in vitro and in vivo studies that suggest that iron absorption is in-

creased with exocrine pancreatic deficiency^{4,5} and that the administration of pancreatic enzymes may impair oral iron absorption.⁶⁻⁸ Other investigators, however, have not confirmed an effect of pancreatic enzymes on iron absorption.⁹ The purpose of the present study was to investigate iron absorption in young-adult patients with CF and age-matched control patients as well as to measure the effect of a preparation of pancreatic enzymes on iron absorption.

PATIENTS AND METHODS

Patients

Thirteen patients with CF under medical care at The Johns Hopkins Hospital CF Center, Baltimore, Md, and 9 age-matched control patients participated in the study. The control patients were recruited from the medical and nursing staff at the hospital. The study was approved by the Joint Committee on Clinical Investigation of The Johns Hopkins Medical Institutions, and informed written consent was obtained from all subjects. The diagnosis of CF was based on a characteristic clinical picture and two positive quantitative pilocarpine iontophoresis sweat test results. Patients were invited to participate irrespective of their hematologic status. The patients had not experienced a pulmonary exacerbation in the preceding month. None of the subjects had evidence of cor pulmonale, diabetes mellitus, or hepatobiliary or renal disease, nor were they receiving oxygen or drugs known to affect gastric emptying. Among the patients with CF, 11 were taking pancreatic enzyme supplements regularly and 1 was receiving a therapeutic dosage of iron.

Methods

Serum ferritin levels were measured by an immunoradiometric assay (Biorad, Hercules, Calif) and expressed in micrograms per liter (normal, >12.5 µg/L). Serum erythropoietin levels were determined by a radioimmunoassay (Smith Kline & French Laboratories, Philadelphia, Pa) and expressed in units per liter (normal, 4 to 26 U/L). Serum iron levels were measured by a ferrozine assay¹⁰ and expressed in micromoles per liter (nor-

mal, 11.6 to 31.3 µmol/L). Oxygen saturation was determined by pulse oximetry (Nellcor Inc, Hayward, Calif) with the subjects awake and resting. Hemoglobin levels, hematocrit values, red blood cell distribution widths, and mean corpuscular volumes were determined by standard methods.

Studies to determine the absorption of iron given orally were performed by a modification of the method of Crawley.¹¹ After a 12-hour overnight fast during which no medications were given, an intravenous heparin lock was placed, and an early morning venous blood sample was collected for baseline hematologic values. On the first day of the study, elemental iron (2 mg/kg) was administered in the form of liquid ferrous sulfate (25 mg of iron per milliliter), and serum iron levels were measured 1, 2, and 3 hours after iron administration. Within 1 week the protocol was repeated, but in the second study the subjects were given four capsules of a pH-sensitive, enteric-coated, microsphere preparation of pancrelipase (Pancrease, McNeil Pharmaceutical, Spring House, Pa) 1 hour prior to the administration of iron. The mean interval between studies was 3.6 days for the patients and 3.1 days for the controls. No subjects were studied on consecutive days. Absolute increases in serum iron levels as well as percentage increases above baseline were calculated 1, 2, and 3 hours after iron administration. Differences in iron absorption between patients with CF and controls and between subjects with low and normal serum ferritin levels were evaluated by independent group *t* tests. The effect of supplemental pancrelipase was evaluated using paired-differences *t* tests. The *t* tests were calculated using separate estimates of variances in instances where the group variances could not be assumed to be equal.

RESULTS

Characteristics of the patients with CF and control patients on entrance into the study are shown in Table 1. They were closely matched in age. One of the patients with CF had an oxygen saturation of 93%; all others had saturations of 95% or above. The patients with CF weighed significantly less than the controls. Baseline hematologic data for the

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From the Department of Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, Md.

Read before the 57th Annual Meeting of the Society for Pediatric Research, Washington, DC, May 4, 1988.

Reprint requests to The Johns Hopkins Hospital, CMSC #2-125, Baltimore, MD 21205 (Dr Rosenstein).

Table 1.—Baseline Data

	Patients	Controls
No. of subjects	13	9
M:F ratio	8:5	7:2
W:B ratio	9:4	9:0
Age, y		
Mean	23.1	25.8
Range	18-41	20-33
O ₂ saturation, %		
Mean	97.1	98.4
Range	93-100	98-99
Weight, kg*		
F	49.0 ± 9.7	57.9 ± 7.5
M†	60.0 ± 7.5	74.4 ± 5.9
Height, cm*		
F	160.3 ± 8.5	162.4 ± 13.2
M‡	170.4 ± 3.9	178.7 ± 8.5

*Values are mean ± SD.

†*P* < .001.‡*P* < .05.

Table 2.—Baseline Hematologic Data*

	Patients	Controls
No. of subjects	13	9
Hemoglobin, g/L	140 ± 13	144 ± 13
Hematocrit	0.421 ± 0.037	0.431 ± 0.047
Mean corpuscular volume, fL	86.1 ± 2.7	90.9 ± 5.0†
Red blood cell distribution width	13.1 ± 0.9	12.6 ± 0.7
Serum iron, μmol/L	11.9 ± 6.3	18.9 ± 5.9‡
Serum ferritin, μg/L	68.1 ± 77.8	64.2 ± 64.6
Erythropoietin, U/L	14.5 ± 4.7	11.6 ± 4.9

*Values are mean ± SD.

†*P* < .001.‡*P* < .05.

patients and controls are shown in Table 2. There was no significant difference in hemoglobin values; the lowest value in either group was 119 g/L. Mean values for red blood cell distribution width, serum ferritin, and serum erythropoietin were similar in patients and controls. However, in 5 patients and 4 controls, serum ferritin levels were less than 25 μg/L. In the patient group, erythropoietin levels ranged from 6 to 20 U/L (mean, 14.5 U/L); there were no elevations. The mean corpuscular volume was significantly lower in patients (86.1 ± 2.7 fL) than in controls (90.9 ± 5.0 fL) (*P* < .001). The mean serum iron concentration was significantly higher in controls (18.9 ± 5.9 μmol/L) than in patients (11.9 ± 6.3 μmol/L) (*P* < .05); 5 of the 13 patients but none of the 9 controls had a serum iron concen-

tration lower than 9 μmol/L. There was no significant difference in baseline mean serum iron levels between study days 1 and 2 in either the patient or control groups.

In the absence of administration of pancreatic enzyme supplements, there was no significant difference in iron absorption between patients and controls (Fig 1). The peak iron level above baseline increased by 311% in the patients and by 230% in the controls (not significant). However, there was significant impairment of iron absorption in both patients and controls after the administration of pancrelipase. In the patient group, 1 hour after iron administration, there was a 62% increase in the serum iron level above baseline in the presence of pancrelipase and a 188% increase above baseline in the absence of pancre-

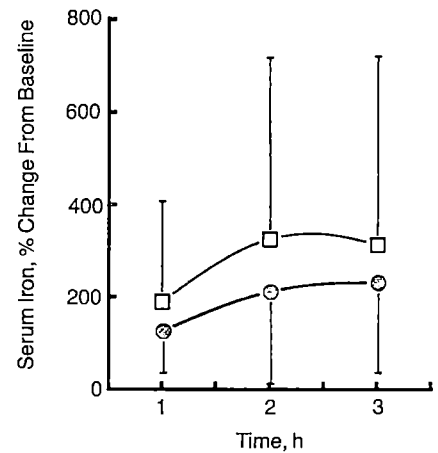


Fig 1.—Percentage increases in serum iron levels in patients (squares, *n* = 13) and controls (circles, *n* = 9) following the oral administration of elemental iron (2 mg/kg) in the absence of pancreatic enzyme supplements (not significant).

lipase (*P* < .05) (Fig 2). In the control group (Fig 3) and in the patient and control groups combined, percentage increases in serum iron levels as well as peak serum iron levels were significantly higher in the absence of pancrelipase 1, 2, and 3 hours after iron administration. When iron absorption in the absence of pancrelipase was compared in the 9 subjects (5 patients, 4 controls) with serum ferritin levels less than 25 μg/L and in the 13 subjects (8 patients, 5 controls) with serum ferritin values greater than 25 μg/L, peak serum iron levels were significantly higher 1, 2, and 3 hours after iron administration (*P* < .02), and the percentage increase in iron levels was significantly higher 2 and 3 hours after iron administration (*P* < .05) in the group with low serum ferritin levels. Among all subjects there was an inverse relationship between baseline serum ferritin levels and iron absorption (Fig 4).

COMMENT

Our results are consistent with previous findings that iron deficiency is common in patients with CF.¹⁻³ We found a significant reduction in iron absorption, both in patients with CF and in controls, when iron was administered along with pancreatic enzymes. This is consistent with previous studies in which administration of pancreatic enzymes has been associated with reduced oral iron absorption in both healthy controls and

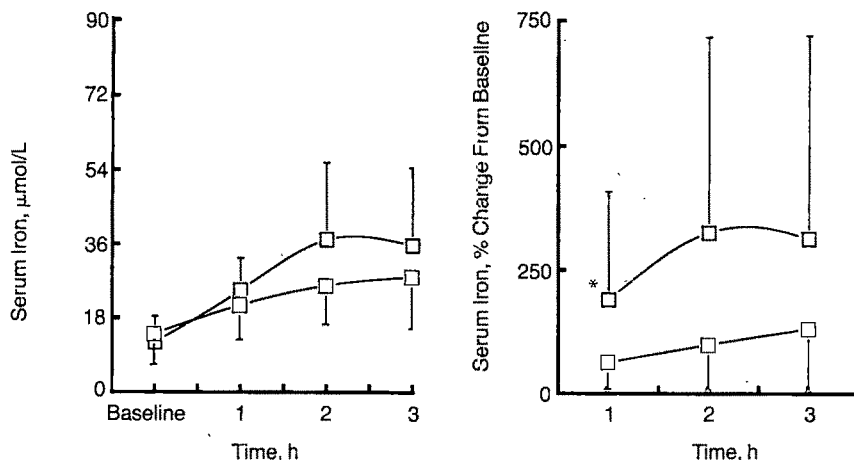


Fig 2.—Comparison of absolute increases in serum iron levels (left) and percentage increases above baseline (right) in the absence (open squares) and presence (solid squares) of pancreatic enzyme supplements in 13 patients with cystic fibrosis. Asterisk indicates $P < .05$.

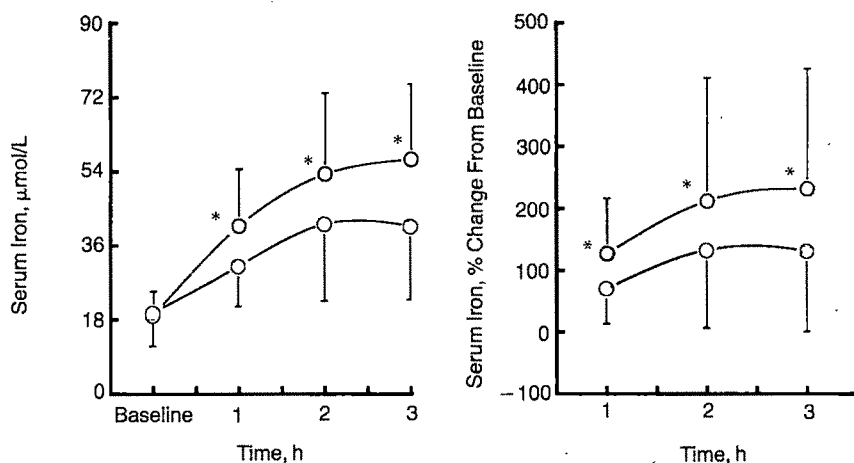


Fig 3.—Comparison of absolute increases in serum iron levels (left) and percentage increases above baseline (right) in the absence (open circles) and presence (solid circles) of pancreatic enzyme supplements in nine controls. Asterisk indicates $P < .05$.

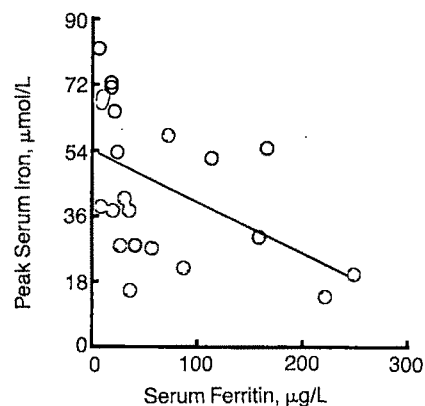


Fig 4.—Relationship between baseline serum ferritin and peak serum iron concentrations measured over a 3-hour period following the oral administration of elemental iron (2 mg/kg) in patients (solid circles, $n = 13$) and controls (open circles, $n = 9$) in the absence of pancreatic enzyme supplements ($r = -.5$, $P < .02$). The solid line represents the linear regression for patients and controls combined.

zymes on pH has also been postulated. In *in vitro* studies it has been shown that the pH of ferrous sulfate alone is lower than that of a ferrous sulfate-pancreatic enzyme mixture.⁷ The more acid pH of ferrous sulfate alone would favor iron solubility and absorption. However, in an isolated rat jejunum model, iron uptake was inhibited by pancreatic enzymes even when the pH was kept constant.⁸ Alternatively, components of pancreatic enzyme preparations may combine with iron and impair its absorption or may directly injure or bind mucosal iron-binding receptors.

The clinical significance of our observations is difficult to interpret. There are two kinds of iron in the diet with respect to the mechanism of absorption: heme iron and nonheme iron. Heme iron is derived from hemoglobin and myoglobin, and nonheme iron is derived mainly from cereals, vegetables, and fruits.¹⁴ Heme iron is much better absorbed than nonheme iron. The iron employed in this study was nonheme iron, but the bioavailability of ferrous sulfate when given with water, as in our study, is usually much greater than when iron in any form is ingested in a meal. The fact that iron deficiency anemia develops in so many patients with CF who are given pancreatic extract supplement suggests that our observations do have biologic relevance. It should be noted, however, that all of our study subjects were

patients with CF.⁴⁷ It has also been observed that patients with CF who had been receiving pancreatic supplements longer than 1 year had lower hemoglobin and plasma iron levels, as well as impaired iron absorption, compared with untreated patients and controls.⁶ Conversely, increased iron uptake has been observed in patients with pancreatitis and pancreatic insufficiency.⁶ Heinrich et al,⁹ in studies on just three patients, found no difference in iron absorption between patients with CF and controls and no effect of enzymes on iron absorption. In animal studies, ligation of the pancreatic duct has led to an in-

crease in iron absorption,¹² and *in vitro* studies using an isolated rat jejunum preparation have demonstrated inhibition of iron uptake following the administration of pancreatic extract.⁸

The mechanism by which pancreatic enzymes impair iron absorption is not clear. Intraluminal pH may be an important factor, since inorganic iron must first be reduced to the ferrous state to be absorbed. Increased absorption of iron would be expected in patients with pancreatic insufficiency because of a lower intraluminal pH, which favors solubility and reduction of iron to the ferrous form.¹³ An effect of pancreatic en-

adults; the results may not be applicable to growing children.

In patients with CF, an inverse relationship between PaO_2 levels and hemoglobin and hematocrit values has been observed,⁷ but compensatory polycythemia is unusual. A defect in red blood cell production appears to be the primary factor, most likely secondary to a disturbance in erythropoietin regulation and iron availability. Erythropoietin levels were normal in our patients. This is consistent with a previous study in patients with CF in which there was no compensatory increase in erythropoietin relative to the degree of underlying anemia and hypoxemia.² This blunted erythropoietin response is similar to that seen in a variety of inflammatory conditions.^{15,16} Its mechanism in patients with CF is not known.

In conclusion, the iron status of patients with CF should be routinely monitored; the serum ferritin level is proba-

bly the most useful measurement of total body iron stores. Based on our results, we recommend that if supplemental iron is given, it should not be administered in close proximity to administration of pancreatic enzyme supplements.

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Sandra Zubrowski assisted in the preparation of the manuscript.

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In Other AMA Journals

ARCHIVES OF OPHTHALMOLOGY

Retinopathy of Prematurity: Problem and Challenge

(Flynn, Phelps, eds)

Reviewed by Robert A. Peterson, MD (*Arch Ophthalmol*. 1989;107:967)

The Battered Child. 4th ed.

(Helfer, Kempe, eds)

Reviewed by David Walton, MD (*Arch Ophthalmol*. 1989;107:967)

Risk of Infectious Complications in Well-Appearing Children With Transient Neutropenia

Anthony J. Alario, MD, John S. O'Shea, MD

• To determine whether well-appearing children found incidentally to be neutropenic are at risk for an infectious complication, 44 consecutive months of hematology laboratory records were reviewed. One hundred nineteen patients had medical record documentation regarding clinical course, serial white blood cell counts, and the absence of serious infections, chronic illnesses, or a family history known to be associated with neutropenia. The median duration of documented neutropenia was 13 days (range, 1 to 491 days). Infectious complications occurred in 4 of the 36 patients who had neutropenia for more than 30 days (2 with stomatitis, 1 with cellulitis, and 1 with pneumonia) but in none with shorter durations of neutropenia. There were no significant associations between the development of an infectious complication and either the initial absolute neutrophil count or the lowest documented absolute neutrophil count, nor was there a correlation between the initial absolute neutrophil count and the duration of neutropenia. These data indicate that infectious complications occur in otherwise well children with unexplained neutropenia that persists, but these infections are infrequent and usually are superficial.

(AJDC. 1989;143:973-976)

It is well recognized that children and adults with a chronically suppressed immune system are at an appreciable risk for developing septicemia or a serious focal infection while they remain immunocompromised.^{1,2} In addition, individuals with chronic or immune-mediated neutropenia are also susceptible to mucocutaneous and pyogenic infec-

tions.³⁻⁶ This susceptibility may be particularly evident in childhood, when the other modalities of host defense are not mature.³ The risk of infection in these situations is correlated with both the duration and the degree of neutropenia.^{3,7-9}

Even though isolated neutropenia is common in children who were previously well,¹⁰ pediatricians often become concerned that these children may be at the same significant risk for infection as those who are immunocompromised.^{10,11} The purpose of this study was to determine whether well-appearing children without identified comorbid illness who are found to be neutropenic during minor acute illnesses, routine preoperative screening, or treatment for common childhood conditions are at risk for an infectious complication while they are neutropenic. An additional study purpose was to define the relationships between the duration of neutropenia, the initial and lowest documented absolute neutrophil counts, and the development of infectious complications in this cohort of children.

PATIENTS AND METHODS

Patient Sample and Clinical Data Gathering

Forty-four consecutive months of hospital hematology records for all patients 18 years or younger were reviewed to identify retrospectively children with neutropenia, defined as an absolute neutrophil count of $1.5 \times 10^9/L$ or less^{8,10,12} (absolute neutrophil count = total leukocyte count per microliter \times percentage of neutrophils and bands $\times 0.001$). In addition, 20 children with an absolute neutrophil count of $1.5 \times 10^9/L$ or less were prospectively identified by daily review of hematology records from either the pediatric outpatient (the primary care unit and emergency department) or the inpatient (wards and intensive care unit) services. Complete blood cell counts were performed on one of two cell counters (Coulter Model S

or S-Plus, Coulter Electronics, Inc, Hialeah, Fla). Leukocyte differential counts were determined by licensed technologists who performed microscopic examinations of 100 cells on the peripheral blood smears. The medical records of all neutropenic patients were then extracted by means of a standard form to record demographic information, the clinical circumstances associated with neutropenia (ie, presenting complaints, history and physical examination findings, and initial and final diagnoses), and the clinical outcome, including the development of any infectious complication. In this study, an infectious complication was defined as a mucocutaneous or systemic bacterial or fungal infection that occurred while the patient was neutropenic. Additionally, the degree and duration of neutropenia and associated laboratory results (including blood, urine, cerebrospinal fluid, and skin cultures and bone marrow examinations) were recorded. The physicians of patients who lacked complete hospital record data on medical outcome were contacted by telephone or letter by a research assistant, for follow-up information.

Patients who were previously well and had isolated neutropenia documented during an acute, febrile illness were included. Children who had received a complete blood cell count as part of a routine screening protocol before elective surgical procedures were included as well, if they did not have a presurgical condition or syndrome known to be associated with neutropenia. Patients were also included if they had been receiving either antimicrobials for acute, self-limited common pediatric illnesses (eg, otitis media or pharyngitis) or anticonvulsants for well-defined seizure disorders and had undergone treatment at least 48 hours during the 2 weeks before the documentation of neutropenia.

Patients with a family history of a neutrophil disorder or with previously documented cyclic, autoimmune, or chronic neutropenia, pancytopenia, or chronic illnesses associated with immune suppression (eg, malignant neoplasm, human immunodeficiency virus infection, and chronic renal diseases) were excluded from the study. Patients with a serious bacterial infection (eg, meningitis or

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From the Division of Ambulatory Pediatrics, Department of Pediatrics, Rhode Island Hospital and Brown University, Providence.

Read in part at the 57th Annual Meeting of the Society for Pediatric Research, Washington, DC, May 5, 1988.

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sepsis) diagnosed at the visit when the neutropenia was detected were also excluded. Eligible patients who did not have serial white blood cell counts obtained at least every 21 days until the neutropenia resolved (as documented by a minimum of two blood counts) were analyzed separately from those in whom serial counts were available.

Data Analysis

Data were analyzed by means of a programmed calculator with standard techniques. The χ^2 test was used to analyze data that were categorical, and a χ^2 test for linearity was used for data that were part categorical and part ordinal to determine if relationships were linear.¹³ Pearson's Product-Moment Correlation coefficients were determined for dimensional data.

RESULTS

Records of 251 pediatric patients with an absolute neutrophil count of $1.5 \times 10^9/L$ or less were reviewed. Forty-three (17%) were excluded from fur-

ther analysis because of cyclic neutropenia, pancytopenia, or chronic illnesses (ie, malignant neoplasms) associated with immune suppression. Sixteen children (6%) were excluded because they presented with symptoms and signs of a serious bacterial infection (4 with meningitis, 4 with sepsis, and 8 with pneumonia) at the visit when neutropenia was detected. An additional 73 children (29%) had only clinical outcomes assessed because they did not meet the criterion of having serially documented white blood cell counts; 40 were taking medications known to be associated with neutropenia (mostly antibiotics and anticonvulsants), and 33 had acute illnesses. None of the children in these latter two groups developed an infectious complication at follow-up evaluations. The remaining 119 neutropenic patients had serial white blood cell counts documented for at least every 21 days until the neutropenia resolved, and they form the basis of this report. Sixty-six percent were acutely ill, in 15% neutropenia was detected during routine preoperative screening, and 19% were receiving antimicrobial or anticonvulsant medications known to be associated with neutropenia (Table 1). Thirty-eight percent of the acutely ill patients were initially admitted to the hospital for observation and/or antimicrobial therapy.

The mean age of the 119 patients was 42 ± 28 months, 57% were male, and 52% were white. The mean white blood cell count was $6.337 \pm 2.959 \times 10^9/L$, and the mean absolute neutrophil count was $1.029 \pm 0.498 \times 10^9/L$. Fifty-three percent of the sample had an absolute neutrophil count between 1.01 and $1.5 \times 10^9/L$, 34% between 0.501 and $1.0 \times 10^9/L$, and 13% $0.5 \times 10^9/L$ or less. The median duration of neutropenia for the entire sample was 13 days (range, 1

to 491 days), and the median duration of neutropenia for children with an absolute neutrophil count of 0.5×10^9 or less was 17 days. Neutropenia resolved in 70% of the children by 30 days and in 80% by 42 days. The median percentage of lymphocytes in the peripheral blood of the patients was 0.68 (range, 0.30 to 0.96; mean, 66.4 ± 12.4). The median percentage of monocytes was 0.08 (range, 0.01 to 0.23; mean, 7.5 ± 5.4), and of eosinophils, 0.3 (range, 0 to 0.27; mean, 2.8 ± 2.5). Eleven percent of the children had increased numbers of basophils, myelocytes, metamyelocytes, and plasmacytoid cells in the peripheral smear. Bone marrow examinations were performed in four patients; two had normal marrow cellularity, and the other two had maturation arrest at the promyelocyte or myelocyte stages. There were no racial differences among patients regarding the total leukocyte count, the initial or lowest documented absolute neutrophil count, the duration of neutropenia, or the proportions of lymphocytes, monocytes, or eosinophils. In addition, no correlation was found between the initial absolute neutrophil count and the duration of neutropenia in either white ($r = .185$, $P = .15$) or black ($r = .156$, $P = .20$) ($r_{\text{total}} = .163$, $P = .10$) children.

Four children (3.4%) developed documented infectious complications while they remained neutropenic, all for longer than 30 days (Table 2). No patient had an absolute neutrophil count of $0.5 \times 10^9/L$ or less when an infectious complication was diagnosed. In addition, the documented nadir of the neutrophil count was not correlated with the time of onset of an infectious complication in any of these patients. All of the patients were hospitalized, but none experienced severe morbidity from the infectious complication. Three were

Table 1.—Sample Characteristics (N = 119)

Patient Group	No. of Patients
Acutely ill	78
Illness	
Viral syndrome	43
Asthma/bronchiolitis	9
Otitis media	4
Gastroenteritis	3
Rule out sepsis	3
Epstein-Barr infection	2
Other	14
Neutropenia detected during routine preoperative screening	18
Type of surgery	
Otolaryngologic	11
General	5
Orthopedic	2
Receiving medications associated with neutropenia	23
Type of medication	
Antimicrobial	18
Anticonvulsant	5

Table 2.—Characteristics of Patients With Infectious Complications Diagnosed While Patients Were Neutropenic*

Patient/Age/ Race/Sex	Initial Diagnosis	Initial ANC, $\times 10^9/L$	IC	ANC at Diagnosis of IC, $\times 10^9/L$	Duration of Neutropenia When IC Was Diagnosed, d	Total Duration of Neutropenia, d
1/18 mo/W/M	Viral syndrome	0.756	Stomatitis	1.106	31	32
2/7 y/W/M	Infectious mononucleosis	1.164	Cellulitis	0.920	57	64
3/2 y/B/F	Otitis media	0.850	Pneumonia	1.240	111	123
4/8 mo/B/M	Rule out sepsis	0.388	Stomatitis	1.050	174	181

*ANC indicates absolute neutrophil count; IC, infectious complication.

treated with antimicrobials administered intravenously. All patients improved within 4 to 8 days of hospitalization, and in two cases complete clinical recovery occurred before resolution of neutropenia. No bacterial, fungal, or viral organisms were identified by blood, cerebrospinal fluid, or tissue cultures in any of these children. The absolute neutrophil count rose to over $1.5 \times 10^9/L$ in these patients within 1 to 12 days after diagnosis. None of the children redeveloped documented neutropenia in the several months after the infection. Furthermore, no significant associations between the development of an infectious complication and either the initial ($\chi^2=1.36$, $P=.25$) or lowest ($\chi^2=3.50$, $P=.08$) documented absolute neutrophil count were found.

COMMENT

This study has documented that otherwise healthy children in whom isolated, transient neutropenia is discovered during a minor, acute illness, routine preoperative screening, or treatment for common pediatric conditions are at little risk of developing septicemia or other serious infectious complications. In addition, infections are infrequent, occur in children with neutropenia lasting longer than 30 days, and tend to be superficial (ie, involve the skin and mucous membranes) in a majority of cases. None of these patients developed septicemia or bone or central nervous system infection.

It is fairly common for a pediatrician to encounter a child with isolated, transient neutropenia in many clinical settings. A retrospective review by Bowden et al¹⁴ demonstrated that neutropenia was present in 3% of inpatients and 7% of outpatients. Although one third of our patients had an absolute neutrophil count between 0.5 and $1.0 \times 10^9/L$, documented cases of stomatitis, gingivitis, or skin infections did not occur with the frequency that has been previously reported with counts in this range.¹¹ More importantly, only one of the 16 previously well children with initially severe neutropenia (absolute neutrophil counts $<0.5 \times 10^9/L$) experienced any infectious complication. This patient developed stomatitis after a prolonged period of neutropenia. Valiaveedan et al¹⁶ recently reported on an

almost identical number of patients with severe neutropenia and found bacteremia from commonly identified organisms (*Streptococcus pneumoniae*, *Haemophilus influenzae*) in three patients. The reasons for the relatively high proportion of children with bacteremia, although not discussed, perhaps were related to patient selection, since all of their patients had been hospitalized and evaluated by the hematology service. Combining cases of our series and that of Valiaveedan et al, none of the 33 children with an absolute neutrophil count less than $0.5 \times 10^9/L$ had invasive infections with either *Staphylococcus* or gram-negative enteric organisms as are commonly encountered in immunosuppressed patients with severe neutropenia.¹⁰

One half of the patients in our series were black, suggesting that possibly some had "pseudoneutropenia" or "benign neutropenia." This phenomenon has been identified in a proportion of the 20% to 30% of blacks with a significantly lower mean total white blood cell count than whites.¹⁶⁻¹⁸ However, the distribution of the absolute neutrophil count in black children in our series paralleled that of white children, and the duration of neutropenia in both black and white children was similarly transient and consistent with a previous report.¹⁵ In addition, all of the black children had an absolute neutrophil count greater than $1.5 \times 10^9/L$ at follow-up determinations. Therefore, black children with transient neutropenia do not appear to be at any different risk for the development of serious infections than are white children. The question of whether there is a subset of black children with an absolute neutrophil count chronically in the neutropenic range and thus at potential risk for serious infections is not addressed by this study.

There are certain limitations of this study that may affect the interpretation of the data. The timing of serial blood counts was usually up to the discretion of the patient's physician. Therefore, the precise duration of neutropenia for any given patient is unknown. However, a median duration of neutropenia of 13 days clearly indicates that it was transient in a large number of cases. While there did not appear to be any relationship between the subsequent

development of an infectious complication and either the initial or lowest absolute neutrophil count, the number of patients with severe neutropenia was small and the duration of neutropenia relatively transient. It is possible that this degree of neutropenia is not commonly detected in essentially well children.

The mechanisms by which many acute childhood illnesses (eg, parvovirus infection) induce transient neutropenia are incompletely understood. It is postulated that neutropenia in these situations may be the result of a number of processes, including excessive neutrophil margination along endothelial surfaces, complement activation of C5 to C5a, an increase in the peripheral utilization or destruction of leukocytes, endotoxin depletion of the bone marrow reserve pool, or suppression of myelopoiesis by the infecting agent.^{8,10-12} Another possible mechanism for the induction of neutropenia is a transient production of circulating antineutrophil autoantibodies.^{6,19} Both toxic and immunologic mechanisms for drug-induced neutropenia have been described in detail elsewhere.^{11,20,21}

Overall, the small number of patients experiencing an infectious complication paralleled previously reported patterns of skin, mucous membrane, and pulmonary infections seen in children with other forms of neutropenia.^{4,19} The four patients with complications had benign courses and had normal neutrophil counts within 2 weeks of the onset of complications. The recovery from neutropenia may have been coincidental with the infection or related to such factors as waning antineutrophil antibodies or a direct effect of the infection in stimulating the bone marrow. The majority of patients in this sample had an increase in the mean proportion of lymphocytes, monocytes, or eosinophils, often in ranges that were greater than expected for age.¹² Whether the increase in circulating lymphocytes and other granulocytes had a protective effect against invasion of microorganisms is unknown. The commonly encountered peripheral-blood monocytosis in many neutropenic states may offer only nominal protection against pyogenic organisms, since the response of monocytes to chemotactic stimuli and their

rate of phagocytosis are more sluggish than are those of polymorphonuclear leukocytes.²²

The clinical implication for practitioners is that otherwise well children with neutropenia are unlikely to develop serious infectious complications, especial-

ly if the neutropenia is transient. In most cases, these patients do not require an extensive laboratory evaluation to identify potential pathogens and/or institution of empiric antimicrobial therapy, as has been suggested by some authors.^{10,23} Instead, diligent ob-

servation and frequent follow-up are probably quite efficient courses of management for these patients.

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In Other AMA Journals

JAMA

The Economic Impact and Multiplier Effect of a Family Practice Clinic on an Academic Medical Center

R. Schneeweiss, K. Ellsbury, L. G. Hart, J. P. Geyman (*JAMA*. 1989;262:370-375)

Maternal Mortality in Developing Countries

A. Rosenfield (*JAMA*. 1989;262:376-379)

Pulmonary Hypertension and Asthma in Two Patients With Congenital Heart Disease

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• **Reactive airway disease has only rarely been associated with pulmonary hypertension. We treated two patients with congenital heart disease and asthma who had increased pulmonary arterial pressure at cardiac catheterization. Pulmonary hypertension could not be explained solely by the cardiac lesion, nor by respiratory mechanical factors, as the patients did not have wheezing during the catheterization study. After long-term treatment with bronchodilators, corticosteroids, and oxygen, and coincident with improvement in the airway disease, there was catheterization-proved diminution of pulmonary hypertension. Whether asthma and pulmonary hypertension were causally linked is unknown, but further work seems indicated to elucidate the relationship between bronchoconstriction and pulmonary vasoconstriction. Furthermore, aggressive management of even mild reactive airway disease may be warranted in patients with pulmonary hypertension, regardless of apparent cause.**

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Pulmonary hypertension and cor pulmonale are common sequelae in patients with severe chronic obstructive lung disease, upper airway obstruction, and bronchopulmonary dysplasia.^{1,2} However, pulmonary hypertension has rarely been described in association with asthma. There are a few case reports of the association of pulmonary hypertension and reactive airway disease in adults³⁻⁵ and children,^{6,7} but most of the patients had moderate to severe hypoxemia or polycythemia. In this article, we describe two patients with congenital heart disease, pulmonary hypertension, and asthma but no significant hypoxemia, acidosis, or polycythemia.

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Pulmonary hypertension was documented when the patients did not have significant wheezing but were in a period of their lives when they were having significant asthmatic attacks. With long-term treatment for and amelioration of their airway disease, they had a catheterization-proved decrease in pulmonary arterial pressure.

PATIENT REPORT

PATIENT 1.—A male patient with pulmonary atresia, malalignment ventricular septal defect, and multiple aortopulmonary collaterals underwent placement of a right ventricular to pulmonary arterial valved homograft, patch closure of the ventricular septal defect, and coil embolization of the aortopulmonary collaterals at 16 months of age. Postoperative catheterization (1 month later, to coil another aortopulmonary collateral) revealed a pulmonary arterial pressure of 30/10 mm Hg (one third of systemic pressure). On routine follow-up recatheterization at 26 months of age, he had suprasystemic pulmonary arterial pressure unresponsive to 100% oxygen (Table). The pulmonary arteries were large and without evidence of peripheral stenosis. When catheterized, he did not have significant cyanosis, coughing, wheezing, or respiratory distress. A chest roentgenogram showed moderate cardiomegaly and hyperinflation but no edema or infiltrates.

During the next 4 months he was admitted to the hospital three times in status asthmaticus, twice requiring endotracheal intubation. The wheezing and respiratory distress responded to intravenous isoproterenol hydrochloride, theophylline, and corticosteroids. In the following year he was treated at home with oxygen, albuterol, metaproterenol sulfate, theophylline, cromolyn sodium, and corticosteroids. He had virtual resolution of his airway disease, and all drugs, except oral albuterol, were stopped by 40 months of age. He was recatheterized at 45 months of age, and the pulmonary arterial pressure had decreased to nearly normal levels (Table).

PATIENT 2.—A male patient with double inlet left ventricle, subaortic outflow cham-

ber, restrictive bulboventricular foramen, and severe tubular hypoplasia of the aortic arch underwent a main pulmonary artery to ascending aorta anastomosis (to provide unobstructed outflow from the ventricle to the aorta), ascending to descending aorta homograft, and a modified right Blalock-Taussig shunt (4-mm polytetrafluoroethylene; Impra) graft from the right subclavian artery to the right pulmonary artery) at 6 days of age. Because of increasing cyanosis, at 9 months of age he was recatheterized, and the mean pulmonary arterial pressure was 10 mm Hg. He then underwent a Glenn anastomosis (the pulmonary arteries were divided near their confluence, the superior vena cava was anastomosed to the right pulmonary artery, and the shunt was left in continuity with the left pulmonary artery).

At 11 months of age he was admitted to the hospital with respiratory distress and facial edema. The chest roentgenogram revealed a normal heart size, a small right pleural effusion, increased pulmonary venous markings, and no evidence of air trapping. At catheterization, he did not have a significant cough or wheezing. He had an elevated right pulmonary arterial pressure, a mean left atrial pressure of 9 mm Hg, and a mean right atrial pressure of 6 mm Hg (Table). Although the left atrial pressure was within normal limits, a blade and balloon atrial septostomy was performed to decrease the pulmonary arterial pressure by lowering the left atrial pressure. Despite lowering the mean left atrial pressure to 6 mm Hg, the mean pulmonary arterial pressure decreased only to 21 mm Hg. Later during that hospitalization, the patient developed wheezing, which responded to metaproterenol, cromolyn, and oxygen. He was discharged from the hospital receiving nebulized metaproterenol and cromolyn and did not have any more episodes of significant wheezing.

At recatheterization at 14 months of age, the pulmonary arterial pressure had decreased to a mean of 13 mm Hg (Table).

COMMENT

Although pulmonary hypertension and cor pulmonale have been documented during acute asthmatic episodes,³⁻⁸ pulmonary hypertension seems

Cardiac Catheterization Data*															
	% Oxygen	Pressures, mm Hg				Saturations, %					PVR/SVR, WU	pH	Pco ₂ , mm Hg	Hct	
		PA†	Ao†	PCW (Mean)	RA (Mean)	PA	Ao	PV	SVC	Qp/Qs					
Patient 1															
Initial catheterization (age, 26 mo)	21	128/40 (72)	108/75 (90)	13	11	62	88	...	62	1	17/23	7.36	45	0.45	
	100	116/35 (65)	96/52 (72)	13	11	88	100‡	1	13/14	
Later catheterization§ (age, 45 mo)	21	35/12 (21)	97/54 (72)	11	6	65	92	...	65	1	4/25	7.35	48	0.35	
Patient 2															
Initial catheterization (age, 11 mo)	21	(RPA, 26)	100/55 (72)	9	6	RPA, 67	67	92	41	7.35	43	0.44	
Later catheterization§ (age, 14 mo)	21	(RPA, 13)	98/60 (78)	9	6	RPA, 68; LPA, 83	83	100	68	7.38	41	0.52	

*Ao indicates aorta; Hct, hematocrit; PA, pulmonary artery; PCW, pulmonary capillary wedge or left atrial; PV, pulmonary vein; PVR, pulmonary vascular resistance; Qp/Qs, pulmonary to systemic flow ratio; RA, right atrium; RPA, right PA; SVC, superior vena cava; SVR, systemic vascular resistance; and WU, Woods units.

†Numbers in parentheses are means.

‡Po₂, 434 mm Hg.

§After improvement in asthma.

||After blade and balloon atrial septostomy, mean RPA pressure was 21 mm Hg.

¶Not calculated because separate right and left pulmonary blood flows were not obtained.

to be infrequent during chronic stable asthma. One report⁶ described three children seen in Denver, Colo, with acute signs and symptoms of asthma, moderate arterial hypoxemia, and catheterization-proved pulmonary hypertension. One of the children died and the other two improved symptomatically (one after moving to a lower altitude), but there was no documentation of reversal of pulmonary hypertension.

In this article, we describe two young patients with congenital heart disease and elevated pulmonary arterial pressure out of proportion to their cardiac defect and age. Pulmonary hypertension was documented at a catheterization when they had no significant wheezing but in a period of their lives when they had significant acute asthmatic attacks. Both patients had documentation of low pulmonary arterial pressure by a previous catheterization, making it even more unlikely that the pulmonary hypertension was linked to the cardiac defect. Other causes of pulmonary hypertension were ruled out; chest roentgenograms did not show evidence of significant lung disease, such as pneumonia or atelectasis. Neither patient had significant respiratory distress when catheterized, minimizing the possibility of significant mechanical effects, such as large swings in intrathoracic pressure.⁹ They did not have sig-

nificantly elevated left atrial pressure or signs of congestive heart failure and, therefore, did not have "cardiac" asthma, nor did they have significant acidosis, hypercapnia, or polycythemia. They did have variable degrees of systemic arterial oxygen desaturation, but only mild pulmonary venous desaturation (Table). However, even after the pulmonary venous saturation was increased acutely with oxygen in patient 1, the pulmonary vascular resistance did not decrease significantly. Even though these patients did not have significant wheezing when catheterized, patient 1 had episodes of status asthmaticus within a month of the procedure, and patient 2 developed wheezing during that hospitalization and required bronchodilator treatment after discharge from the hospital. Both patients had a strong family history of asthma.

The coexistence of pulmonary hypertension and bronchoreactive airway disease raises several possibilities. First, it is possible that the pulmonary hypertension and asthma were fortuitously and not functionally associated. However, spontaneous resolution of pulmonary hypertension outside the newborn period is exceedingly rare.¹⁰ There was no intervening surgical or catheterization procedure to cause the decrease in pulmonary arterial pressure. Furthermore, the treatment given for asthma

did not include any conventional drugs used to treat pulmonary hypertension. However, an effect by these agents on the pulmonary vasculature cannot be ruled out, since it has been shown that aminophylline¹¹ and cromolyn¹² can inhibit hypoxic pulmonary vasoconstriction, and long-term oxygen therapy was beneficial to patients with pulmonary hypertension and chronic obstructive lung disease.¹³

Alternatively, the pulmonary hypertension and asthma may have been functionally associated, especially since they occurred simultaneously, and the decrease in pulmonary arterial pressure was concomitant with improvement in the airway disease. Since both bronchi and pulmonary vessels contain smooth muscle in their walls and are in close anatomic relation, release of mediators that cause both bronchoconstriction and vasoconstriction may be involved. Among these potential mediators are histamine,^{14,15} prostaglandin D₂,^{16,17} prostaglandin F_{2α} and thromboxane A₂,^{18,19} and leukotrienes C₄ and D₄.¹⁵ Indeed, pulmonary vasoconstriction and bronchoconstriction are known to be temporally associated and possibly caused by the same mediator(s) in patients with pulmonary thromboembolism.²⁰ In further support of this association between bronchial and vascular disease is a report of 10 adult patients with idiopathic

pulmonary hypertension, 8 of whom had decreased airflow on pulmonary function tests.²¹ Although the fact that our patients were not wheezing when they were catheterized might argue against this possible association, differential bronchial and vascular smooth-muscle sensitivity to the mediators and proximity to the site of release might explain the differing bronchial and vascular responses at a certain point in time.

A third possibility is that there are

individuals with hyperreactive bronchial and vascular smooth muscle, who will abnormally respond to "normal" levels of circulating agents or triggering stimuli with bronchoconstriction and vasoconstriction. One report described a group of patients with concomitant systemic and pulmonary arterial hypertension, raising the possibility of a common mediator or shared hyperreactivity of two different smooth-muscle cell tissues.²² There is also evidence that

smooth-muscle hyperreactivity is an important component in the pathogenesis of essential hypertension.²³

Although this report does not establish a causal relationship between asthma and pulmonary hypertension, it does suggest that this association should be sought in other patients with a similar presentation. Furthermore, aggressive treatment of even mild reactive airway disease may be indicated in patients with pulmonary hypertension.

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In Other AMA Journals

JAMA

Adolescent Pregnancy and Its Consequences

E. R. McAnarney, W. R. Hendee (*JAMA*. 1989;262:74-77)

The Prevention of Adolescent Pregnancy

E. R. McAnarney, W. R. Hendee (*JAMA*. 1989;262:78-82)

Hormonal Therapy for Cryptorchidism With a Combination of Human Chorionic Gonadotropin and Follicle-Stimulating Hormone

Success and Relapse Rate

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• We treated 163 patients (Tanner stage I), aged 1 to 11 years, with cryptorchidism with a combination of 500 to 2000 IU of human chorionic gonadotropin divided into two intramuscular injections and given weekly and 75 IU of follicle-stimulating hormone once a week for 6 weeks. One hundred twelve patients had unilateral cryptorchidism. Response to therapy, which is descent of testes into scrotum, by age group was as follows: 2 (13.3%) of 15 patients aged 1 to 2 years; 8 (29.6%) of 27 patients aged 3 to 4 years; 13 (38.2%) of 34 patients aged 5 to 6 years; and 18 (50%) of 36 patients aged 7 to 11 years. Fifty-one patients had bilateral cryptorchidism. Response by age group was as follows: 1 (16.6%) of 6 patients aged 1 to 2 years; 3 (27.2%) of 11 patients aged 3 to 4 years; 6 (37.5%) of 16 (plus unilateral descent in 1 patient) aged 5 to 6 years; and 10 (55.5%) of 18 patients aged 7 to 11 years. The results are comparable with those obtained with human chorionic gonadotropin treatment alone. A relapse rate of 9.7% after 18 months of follow-up seemed to be lower compared with those reported with treatment with gonadotropin-releasing hormone or treatment with human chorionic gonadotropin alone.

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Cryptorchidism is found in 3% to 4% of full-term newborn infants. This figure for the physiologic phenomenon of late spontaneous migration, which is probably due to the testosterone rise in the first 3 months of life,¹ falls to about 1% at 1 year of age and does not change

in the years that follow.² At any rate, a periodic reexamination of the scrotum is necessary throughout a patient's childhood to document testicular reascent.³ It has been recently stressed that the testes should descend into the scrotum at an early age because after 2 years of age degeneration of the germinal epithelium with loss of spermatogonia of undescended testes has already been demonstrated,^{4,5} even if the real effectiveness of an early successful treatment in preventing later infertility^{6,7} must be proved. Nevertheless, before age 4 years the conventional hormonal treatment with human chorionic gonadotropin (HCG) is of limited usefulness,^{8,9} and treatment with intranasal gonadotropin-releasing hormone presents a high relapse rate independent of the patient's age.¹⁰ Moreover, an early orchiopey may be associated with an increased risk of testis atrophy.¹¹ Follicle-stimulating hormone (FSH) seems to play a role in testicular descent probably by enhancing luteinizing receptors in Leydig's cells and increasing intratesticular testosterone levels.¹²⁻¹⁸ Our study reports the results of using HCG and FSH together in the treatment of cryptorchidism and 18 months' follow-up data of the patients who had had descent of the testes into the scrotum at the end of treatment.

PATIENTS AND METHODS

We treated 163 boys aged 12 months to 11 years. All of them had true unilateral or bilateral cryptorchidism with intra-abdominal (nonpalpable), inguinal (palpable), or pre-scrotal testes. Patients with retractile testes, ectopic testes, anorchia, gonadotropin

deficiency, partial androgen resistance, testicular dysgenesis, and other endocrine or anatomic anomalies were excluded. All the children were prepubertal (Tanner stage P1¹⁹). Of the 163 children, 112 had unilateral cryptorchidism (65 on the right, 47 on the left) and 51 had bilateral cryptorchidism for a total of 214 retained testes. The children were divided into four groups according to age (1 to 2, 3 to 4, 5 to 6, and 7 to 11 years). Written informed consent was obtained. Each subject was treated with a combination of HCG and FSH (either human menopausal gonadotropin [HMG] or purified FSH) according to the following posologic schedule: 500 IU of HCG plus 75 IU of FSH per week (for 6 weeks) for patients younger than 2 years of age; 1000 IU of HCG plus 75 IU of FSH per week (for 6 weeks) for patients between the ages of 2 through 6 years; and 2000 IU of HCG plus 75 IU of FSH per week (for 6 weeks) for patients older than 6 years. The weekly dose of HCG was administered in two intramuscular injections—FSH once a week in combination with HCG. Purified FSH only was used in the group of children 1 to 2 years of age; no difference between the response to HMG or purified FSH was observed in the other age groups.

Once a week for 6 weeks, each child was seen and the position of the testes and side effects were recorded. The results of hormonal treatment were clinically evaluated at the end of the treatment and 4 months later to exclude temporarily positive results. The patients in whom the therapy was successful were also evaluated 18 months after the end of the treatment. When responses were not successful, a surgical correction followed. Statistical analysis was carried out using a χ^2 test.

RESULTS

By associating HCG and FSH, a complete descent at the end of treatment was noted in 36.6% of unilateral and in

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Treatment of Cryptorchidism With Human Chorionic Gonadotropin and Follicle-Stimulating Hormone*

	Unilateral Cryptorchidism (n = 112)					Bilateral Cryptorchidism (n = 51)				
	Group by Age, y					Group by Age, y				
	Total	1-2	3-4	5-6	7-11	Total	1-2	3-4	5-6	7-11
At the end of treatment	36.6	13.3	29.6	38.2	50	39.2	16.6	27.2	37.5	55.5
After 4 mo	33.9	6.6	29.6	38.2	44.4	35.2	16.6	18.1	37.5	50
After 18 mo	33	6.6	25.9	38.2	44.4	35.2	16.6	18.1	37.5	50

*Values are expressed as percent of mean success rate.

39.2% of bilateral cryptorchid testes (Table). This difference was statistically insignificant. Altogether, 82 (38.3%) of 214 testes descended into the scrotum, 3 (13%) of 23 were testes not palpable before the treatment, 66 (37.3%) of 177 were inguinal palpable testes, and 13 (92.8%) of 14 were testes located at the scrotal neck. Among inguinal palpable testes the results were better in that they could be brought into the scrotum or to the scrotal neck. Twenty-nine testes (13.5%) improved their position but did not descend completely, and 103 testes (48.1%) did not respond to the treatment.

There was no different response to therapy between right-sided or left-sided cryptorchid testes. Four months after the end of therapy, relapses occurred in 8.5% (7/82) of the testes (3 patients with unilateral cryptorchidism and 3 patients with bilateral cryptorchidism—1 showed bilateral relapse, and 2 patients showed unilateral relapse, 1 of which occurred after unilateral descent) in which the therapy was successful and the success rate dropped to 33.9% of unilateral and 35.2% of bilateral cases (Table). After 18 months of follow-up, recurrences were found in another patient (who had unilateral cryptorchidism) (relapse rate: 9.7%, 8 of 82 testes) with a further reduction in the success rate of unilateral cryptorchid testes (33%) (Table).

The best results were obtained in children older than 6 years of age with both unilateral (50% at the end of therapy, 44.4% after 18 months) and bilateral (55.5% at the end of treatment, 50% after 18 months) cryptorchidism (Table). In the group of children 5 to 6 years of age, complete descent was observed in about one third of the patients (unilat-

eral, 38.2%; bilateral, 37.5%). In the group of children 3 to 4 years old, complete descent was noted in 29.6% of children with unilateral cryptorchidism (one relapse occurred after 18 months and success rate was 25.9%), and of 27.2% of bilateral cryptorchid testes, there was one relapse after 4 months—a success rate after 18 months of 18.1%. In the group of children 1 to 2 years of age, only 2 patients with unilateral (13.8%) and 1 patient with bilateral (16.6%) cryptorchid testes have had complete descent into the scrotum. One patient with unilateral cryptorchidism had the relapse after 4 months and, therefore, the success rate dropped to 6.6%. Slight side effects were noted and included a small increase in the size of the penis in 22 children (13.5%), spontaneous erections in 14 children (8.6%), and irritability during the treatment in 7 children (4.3%).

COMMENT

Experimental and clinical data suggest that FSH can play an important role in modulating the testosterone secretion of the testes. Follicle-stimulating hormone probably plays the role of increasing luteinizing hormone receptor density in Leydig's cells and stimulating the secretion rate of androgen-binding protein by Sertoli's cells with accumulation of intratesticular testosterone.¹²⁻¹⁸

Our results with combined hormonal therapy (HCG and FSH) are quite similar to those found in studies on the use of this association²¹⁻²² and also to those obtained by using HCG alone.^{8,23-26} Moreover, it is difficult to compare the results of different studies for the variation in dosages, the differences in the selection of patients, and the lack of follow-up data.

Apart from the problem of the insertion of retractile testes in our series, an important aspect to be considered is the position of the testes before the treatment. The worst results are obtained in abdominal retention, as can be seen in the patients in our study. Very good results are obtained in inguinal position, and even better results are obtained in prescrotal position with complete descent in 92% to 99% of the patients.^{23,28} Moreover, it has been noted that among the inguinal palpable testes, the more mobile they are (that is, the ones that could be brought into the scrotum or just above it), the better they respond to the treatment.²⁶ In reference to the therapeutic failures according to Bierich,²⁹ the operation in our patients pointed out ectopia that were not clinically seen before in about 20% of the patients with cryptorchidism.

Our findings emphasize that it is difficult to detect ectopia in all of the patients before treatment, and many patients appear to be unresponsive to hormonal treatment for this reason. Another important factor is the unilateral or bilateral form of cryptorchidism. From our data it can be said that good results were obtained both in unilateral and bilateral cases, even if a slightly higher percentage of success was noted in the latter. However, the difference is not significant. Our data demonstrate that in patients with unilateral and bilateral cryptorchidism, better results were obtained in older children (older than 6 years of age). However, recent studies^{4,6} have shown that histological damages with reduction in the number of spermatogonia have even appeared in 2-year-old patients. It is clearly unnecessary to treat these children earlier.

Nevertheless, by evaluating the results obtained in the group of children 1 to 2 years of age, the success rate after 18 months of follow-up was only 6.6% in cases of unilateral and 16.6% in cases of bilateral cryptorchidism. Therefore, the combination of HCG and FSH seems no more effective than HCG alone in patients younger than 3 years of age,⁶ and it is of limited usefulness in producing testicular descent in the group of patients who are 1 to 2 years of age to facilitate optimum potential for fertility.

An important problem to be consid-

ered is the relapse rate after successful therapy. Reevaluations of the success rate 6 to 12 months after the end of the treatment with HCG are generally lacking. Bierich²⁷ reported a relapse rate 6 months after the treatment of about 30% in all his series and of 40% to 50% between 0 and 10 years of age. The same or higher percentage of relapses was seen after gonadotropin-releasing hormone therapy.^{18,28-30} Combined therapy with gonadotropin-releasing hormone and HCG was able to reduce the recurrence rate to about 10% after 6 months,^{17,18} and our relapse rate with combination therapy of HCG and FSH was only 9.7% after 18 months of follow-up. Gonadotropin-releasing hormone probably induced FSH stimulation. Follicle-stimulating hormone adminis-

tration may also increase responsiveness to luteinizing hormone-enhancing luteinizing hormone receptor population in Leydig's cells or the amount of Leydig's cells recruited from fibroblasts.^{12-14,18} Follicle-stimulating hormone also stimulates the formation rate of androgen-binding protein, which will increase intratesticular testosterone levels.^{14,15} If testicular descent occurs, however, even though it may be transient, it can be predicted that permanent descent will occur at puberty.³¹

In conclusion, our data showed that the combination therapy of HCG and FSH provided good results in the treatment of cryptorchidism without any important side effects. In patients younger than 3 years of age it is ineffective. At present the best age for the combina-

tion treatment of HCG and FSH seems to be in patients who are 3 to 4 years old. This is a compromise between the histological alterations that do not seem serious and a better response to the therapy at this age. Of course, only the follow-up of these patients treated earlier with the combined therapy will be able to confirm if an improvement of fertility can be obtained. The relapse rate after a follow-up of 18 months was only 9.7% of the testes in which the therapy was successful after 6 weeks. The evaluation of the overall results 4 months after the end of the treatment practically rules out only temporarily positive results, even if the follow-up must be carried out much later to guard against the possibility of a late relapse.

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Photographic Cures for Dermatologic Disorders

William E. Slue, Jr (*Arch Dermatol.* 1989;125:960-962)

Neonatal Hyperbilirubinemia at High Altitude

Cynthia Leibson, PhD; Mark Brown, MD; Steve Thibodeau, PhD; David Stevenson, MD; Hendrik Vreman, PhD; Ron Cohen, MD; Gisela Clemons, PhD; Wayne Callen, MD; Lorna Grindlay Moore, PhD

• A previous retrospective study showed an increased frequency of neonatal hyperbilirubinemia at high altitude in Colorado. In a prospective study we found that 39% of newborns at 3100 m altitude vs 16% at 1600 m exhibited hyperbilirubinemia, defined as a day 3 serum bilirubin level of 205 $\mu\text{mol/L}$ or higher. Increased bilirubin production at 3100 m vs 1600 m was shown by increased levels of corrected carboxyhemoglobin. This finding was supported by increased erythropoietin and bilirubin values in cord blood and increased hematocrit values at day 3 among infants at 3100 m vs 1600 m. The sustained elevation in bilirubin for breast-fed vs formula-fed infants at 1600 m was observed for both feeding types at 3100 m. The findings suggested that there is a hematologic response to decreased oxygen availability at high altitude, resulting in increased bilirubin production accompanied by delayed bilirubin clearance.

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We observed an increased frequency of neonatal hyperbilirubinemia at higher (3100 m) compared with lower (1600 m) altitude in Colorado in a previous retrospective study.¹ In the present study we compared infants born at 1600 m and 3100 m to determine whether this finding could be confirmed prospectively. If so, we sought to determine the extent to which increased bilirubin production and/or decreased capacity

for clearance were operating at the higher altitude. We considered that an understanding of factors responsible for the increased frequency of hyperbilirubinemia at 3100 m might be informative as to how the transition from fetal to neonatal life was influenced by the reduced oxygen availability of high altitude, as well as to the understanding of neonatal hyperbilirubinemia generally.

SUBJECTS AND METHODS

Subjects

Subjects born at lower altitudes consisted of infants born over a study period of 19 nonconsecutive weeks at Children's Hospital/St Luke's, Denver, Colo, at an elevation of 1600 m. Subjects born at higher altitudes consisted of infants born over a 10-month period at St Vincent Hospital, Leadville, Colo, at an elevation of 3100 m. White, singleton, full-term healthy infants whose parents granted consent were eligible for the study. Full-term births were defined as gestational age between 38 and 41 weeks from The onset of the mother's last menstrual period. Infants were considered healthy when their 5-minute Apgar score was 8 or higher and when their newborn course was uncomplicated by respiratory distress, congenital abnormality, sepsis, or any other conditions requiring transfer from the low-risk nursery. Infants with positive results of either direct or indirect Coombs' test indicative of Rh or blood group incompatibility were excluded. The parents of two infants at each altitude declined consent.

A major part of the analysis involved the comparison of day 3 serum values between the two altitudes. For some of the 58 eligible infants at 1600 m and the 45 eligible infants at 3100 m we were unable to obtain a mean (\pm SEM) blood serum value at 72 ± 12 hours drawn in conjunction with the required phenylketonuria testing, either because of scheduling conflicts ($n=6$ at 1600 m; $n=7$ at 3100 m) or insufficient serum sample ($n=3$ at 1600 m; $n=7$ at 3100 m). Data analysis with these infants, using serum values from day 2 or day 4 and transcutaneous values when no serum was available, gave the same results as analysis without these infants. However,

to assure comparability of the study groups, infants from whom no serum sample was available at 72 ± 12 hours were excluded from the final analysis, yielding a sample size of 41 breast-fed and 8 formula-fed infants at 1600 m and 21 breast-fed and 10 formula-fed infants at 3100 m. Infants at 3100 m received supplemental 24% O_2 before being weaned to room air (mean, 17 ± 3 hours; range, 2 to 120 hours). Infants at both altitudes were followed up by one of us (C.L.). Study procedures were approved by the University of Colorado, St Vincent Hospital, and Children's Hospital Human Subjects Review Committees.

Relevant information on all infants was obtained from medical record review, interview, and measurement and included the following: (1) maternal characteristics: age, education, marital status, gravidity, parity, prenatal events, history of diabetes, history of smoking, blood type, labor and delivery complications, method of delivery, and use and type of obstetric anesthesia; and (2) infant characteristics: blood type, gestational age by date and by physical examination,² Apgar scores at 1 and 5 minutes, birth weight and length, head circumference, presence or absence of bruising, feeding type, frequency of feeds and supplementation, time of first bowel movement and frequency of bowel movement, weight at days 1, 3, and 7, length of hospital stay, and daily exposure to sunlight (on a five-point scale ranging from dark room/no outings to crib by the window/one or more outings).

Methods

Measurements were obtained on cord blood samples for levels of plasma bilirubin, erythropoietin and hematocrit values. Heel capillary blood samples were obtained³ at 72 ± 12 hours (mean, 70.2 ± 0.5 hours at 1600 m and 70.2 ± 1.0 hours at 3100 m) for measurement of serum bilirubin levels, hematocrit values, and carboxyhemoglobin levels. Samples were analyzed for both total and conjugated bilirubin according to the modified Jendrassik-Grof method⁴ using a centrifugal analyzer (Cobas-Bio, Roche Diagnostics, Nutley, NJ) in the same laboratory at Children's Hospital. Samples from Denver infants and day 3 samples from Leadville infants were stored in the dark at 4°C and

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were analyzed within 12 hours of collection. Leadville cord samples were stored at -25°C and were analyzed within 5 days of collection. Samples kept at 4°C for 12 hours were compared with a portion of the same samples stored at -25°C for 5 days and were found to agree well (mean \pm SEM of differences in 19 samples, $0.34 \pm 1.37 \mu\text{mol/L}$; not significant). So that two infants at 1600 m and one infant at 3100 m who underwent phototherapy outside of 72 ± 12 hours were not excluded, the last available bilirubin value before phototherapy was used for these infants.

For nine of the infants in the higher-altitude group, we were unable to collect sufficient serum for bilirubin analysis by the modified Jendrassik-Grof method, and total bilirubin values were determined using the ultramicro spectral method⁶ (American Optical Bilirubinometer, Southbridge, Mass). Spectral values were converted to the equivalent Jendrassik-Grof value with a linear regression equation determined from 28 separate newborn samples analyzed with both the Jendrassik-Grof (y) and spectral methods (x) ($y = 0.944x + 17$; $P = .000$; $S_{y,x} = 8.8$; 95% confidence interval = 0.899, 0.989; 90% prediction interval at $x_{190} = 180 \pm 213$).

Transcutaneous bilirubin measurements were made on days 1, 2, 3, 5, 7, and 14 using the Minolta Jaundice Meter 101 (Air Shields, Hatboro, Pa). Transcutaneous meter readings were highly reproducible (mean \pm SEM of differences between first and second measurements = 0.46 ± 0.09 U; not significant). The meter was calibrated at both lower and higher altitudes by comparing day 3 transcutaneous and serum bilirubin values obtained simultaneously from each infant ($y = 0.9x + 125$; $r = .94$). Six infants were not available for measurement because they received phototherapy (4 at 1600 m on days 3, 5, 5, and 5 and 2 infants at 3100 m on days 3 and 5). All 6 infants were breast-fed.

Hematocrit values were measured using the microcentrifuge technique.⁸ Erythropoietin level was measured by radioimmunoassay.⁶ Laboratory values for interassay and intra-assay variability for this procedure are 9.7% and 8.4%, respectively. The opportunity for carboxyhemoglobin analysis became available after the study at low altitude was nearly completed. Carboxyhemoglobin values were obtained from 8 of the infants born at 1600 m and 17 of the infants born at 3100 m. Samples were analyzed by gas chromatography in the Neonatology Metabolism Laboratory at Stanford University, Palo Alto, Calif.⁷ Blood carboxyhemoglobin values were corrected for ambient carbon monoxide levels.⁸ Ambient air samples were collected at times and locations near where the sampling for each infant was done and were analyzed by gas chromatography.

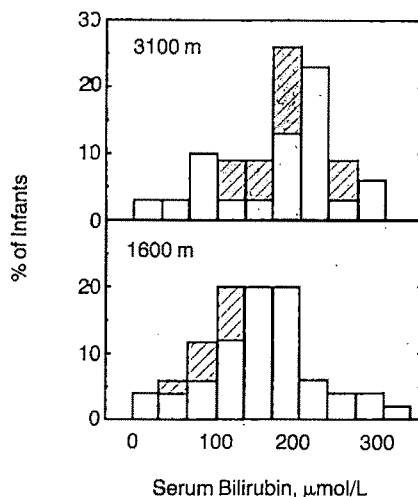


Fig 1.—Distributions of serum bilirubin values at 72 ± 12 hours in infants at altitudes of 3100 m and 1600 m. Shaded areas indicate formula-fed infants.

Statistical Analysis

Measurements were made in duplicate and the average value was recorded. Comparison of values between 1600 m and 3100 m was conducted using unpaired (Student's) t tests, Mann-Whitney U tests, and χ^2 tests. Comparison of bilirubin levels obtained from the same infant at birth and day 3 were performed using paired t tests. Relationships between variables were assessed using linear regression techniques. Results were considered significant when $P \leq .05$. Data are reported as mean \pm SEM.

RESULTS

Neonatal hyperbilirubinemia, defined as a serum bilirubin level of $205 \mu\text{mol/L}$ or higher at 72 ± 12 hours after birth, occurred in 39% (12/31) of the infants born at 3100 m, which was more than twice the 16% (8/49) incidence at 1600 m (Fig 1). The effect of altitude was most apparent in the comparison of formula-fed infants; mean day 3 and transcutaneous bilirubin values for breast-fed infants did not differ between altitudes (Table 1 and Fig 2). However, the proportion of breast-fed infants at 3100 m with bilirubin levels of $205 \mu\text{mol/L}$ or more at day 3 was 2.8 times that for breast-fed infants at 1600 m (10 of 21 at 3100 m vs 7 of 41 at 1600 m; $P < .05$).

We considered the possibility that differences in maternal smoking between altitudes, while not significant, contributed to the finding of higher bili-

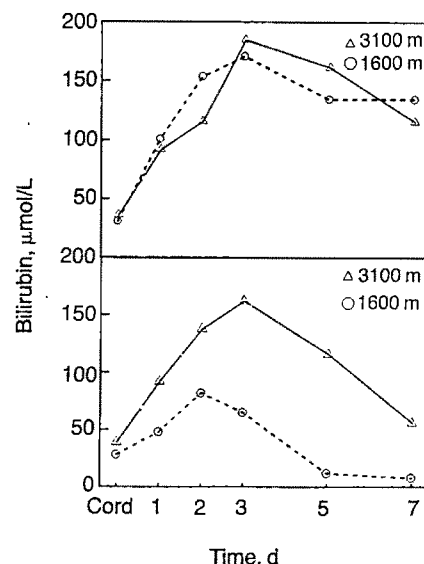


Fig 2.—Median transcutaneous bilirubin values in breast-fed (top) and formula-fed (bottom) infants at altitudes of 3100 m (breast-fed infants, $n = 21$; formula-fed infants, $n = 10$) and 1600 m (breast-fed infants, $n = 41$; formula-fed infants, $n = 8$).

rubin levels among formula-fed infants at 3100 m vs 1600 m. Lower bilirubin values have been reported for infants whose mothers smoke at least one pack of cigarettes a day compared with infants of nonsmoking mothers.⁹ Comparison of formula-fed infants of nonsmoking mothers revealed bilirubin values at day 3 at 3100 m to be $180 \pm 24 \mu\text{mol/L}$ ($n = 9$) vs values at 1600 m of $127 \pm 31 \mu\text{mol/L}$ ($n = 5$; not significant). When all infants of nonsmoking mothers were considered, this difference reached significance ($181 \pm 12 \mu\text{mol/L}$ at 3100 m vs $153 \pm 11 \mu\text{mol/L}$ at 1600 m; $P = .05$). A significant association was found between bilirubin values at day 3 and altitude when adjusted for feeding type, maternal smoking, supplement, and caput/hematoma ($F[1,74] = 3.94$; $P = .05$).

Cord bilirubin values were significantly elevated in infants at 3100 m compared with infants at 1600 m (Table 1). The rise in bilirubin from birth to day 3 measured serially on the same infants was greater at 3100 m than at 1600 m (Δ bilirubin, 154 ± 12 vs $123 \pm 10 \mu\text{mol/L}$; $P < .05$). This difference was apparent when formula-fed but not breast-fed infants were compared (Fig 2). Serial transcutaneous measurements indicated that mean bilirubin values at day 7 for formula-fed infants at 3100 m ($81 \pm 23 \mu\text{mol/L}$; $n = 10$) remained signif-

icantly elevated above cord blood levels, whereas values at day 7 for formula-fed infants at 1600 m (24 ± 12 $\mu\text{mol/L}$; $n=8$) had returned to cord blood levels. Time of peak bilirubin level did not differ between altitudes. Infants at 3100 m exhibited higher carboxyhemoglobin values, higher hematocrit values at day 3, and increased erythropoietin values compared with infants at 1600 m (Table 1).

Comparison of subjects at 1600 m and 3100 m for maternal and infant characteristics showed that the study groups were similar with respect to most risk factors for neonatal hyperbilirubinemia. Values for selected characteristics, including all those for which a significant difference between altitudes was found, are presented in Table 2. As determined from review of maternal histories, none of the mothers were diabetic or exhibited gestational diabetes.

COMMENT

This prospective study confirmed the previous retrospective observation of a more than twofold increase in the proportion of infants with serum bilirubin values at day 3 of 205 $\mu\text{mol/L}$ or more at 3100 m compared with 1600 m in Colorado.¹ The increased proportion of neonatal hyperbilirubinemia was supported by higher cord blood bilirubin values at 3100 m. Infants at high risk for neonatal hyperbilirubinemia (eg, those with positive results of Coombs' test indicative of hemolytic disease and those with conditions requiring transfer from the low-risk nursery) were excluded; therefore, the reported figures may represent minimal estimates of the true frequency of neonatal hyperbilirubinemia at each altitude.

The greater rise in bilirubin values from birth to day 3, higher mean bilirubin values, and sustained elevation of bilirubin values at 3100 m vs 1600 m were observed in the comparison of formula-fed but not breast-fed infants (Table 1 and Fig 2). Although an explanation is not clearly discernible, it is possible that differences in breast-feeding practices between the nurseries may have contributed to this distinction between feeding types. The nursing staff at Children's Hospital/St Luke's (1600 m) promoted frequent breast-feeding and discouraged supplementa-

Table 1.—Comparison of Bilirubin and Hematologic Characteristics at 1600 m and 3100 m*

	Altitude		P†
	1600 m	3100 m	
Total bilirubin, $\mu\text{mol/L}$			
Birth	32 ± 2 (37)	38 ± 2 (23)	.01
72 h	149 ± 9 (49)	178 ± 12 (31)	.06
Breast-fed	156 ± 10 (41)	178 ± 17 (21)	.25
Formula-fed	115 ± 20 (8)	180 ± 14 (10)	.02
Conjugated bilirubin, $\mu\text{mol/L}$			
Birth	6 ± 0 (36)	5 ± 1 (21)	.52
72 h	8 ± 0 (40)	6 ± 1 (11)	.003
Hematocrit			
Birth	0.51 ± 0.01 (28)	0.54 ± 0.01 (27)	.08
72 h	0.54 ± 0.01 (31)	0.62 ± 0.01 (30)	.000
Breast-fed	0.55 ± 0.01 (26)	0.62 ± 0.01 (21)	.000
Formula-fed	0.51 ± 0.03 (5)	0.60 ± 0.02 (10)	.02
Erythropoietin, ln mIU/mL			
Birth	3.6 ± 0.1 (30)	4.0 ± 0.2 (17)	.05
Carboxyhemoglobin, corrected %			
Saturation, STPD, %	0.64 ± 0.06 (8)	1.17 ± 0.14 (17)	.02
Breast-fed	0.59 ± 0.08 (6)	1.17 ± 0.22 (10)	.07
Formula-fed	0.78 ± 0.00 (2)	1.16 ± 0.14 (7)	.31

*Values are given as mean \pm SEM. Numbers in parentheses are sample sizes. ln indicates natural log transformation; STPD, a volume of gas at standard temperature and pressure that contains no water vapor.

†All P values were derived with a two-tailed t test except for those for hematocrit for formula-fed infants, which were derived by the Mann-Whitney U Test.

Table 2.—Maternal and Infant Characteristics at 1600 m and 3100 m*

Characteristic	Altitude	
	1600 m (n=49)	3100 m (n=31)
Maternal age, y	28 ± 1	26 ± 1
Maternal education, y	14 ± 1	13 ± 1
Prenatal care, Nc. of visits	10 ± 0	9 ± 1
Gravidity	2.5 ± 0.3	2.4 ± 0.2
Parity	1.9 ± 0.1	1.8 ± 0.2
Gestational age, wk (by dates)	39.9 ± 0.2	39.8 ± 0.2
Gestational age, wk (by examination)	39.7 ± 0.2	39.9 ± 0.3
Appar score, 1 min	7.8 ± 0.2	7.9 ± 0.2
Appar score, 5 min	9.0 ± 0.1	9.2 ± 0.1
Birth weight, g	3301 ± 58	3126 ± 74
Birth length, cm	50.9 ± 0.3	50.9 ± 0.4
Head circumference, cm	34.2 ± 0.2	33.5 ± 0.2 †
Infant weight gain by day 7, %	0.6 ± 1.1	1.0 ± 1.8
Breast-feeding	41/49	21/31
Supplement (breast-fed only)	20/41	16/21†
Supplements/d (breast-fed only)	0.5 ± 0.1	1.6 ± 0.4 ‡
Frequency of breast-feeding/d	8.5 ± 0.3	7.1 ± 0.4 ‡
Maternal smoking	12/49	2/31
Bowel movements per day	3.2 ± 0.2	3.7 ± 0.2
Caput/hematoma	19/49	4/31†
Weight gain by day 7, %	0.6 ± 1.1	1.0 ± 1.8
Sun exposure, U	3.2 ± 0.1	3.8 ± 0.1 ‡

*Values are given as mean \pm SEM.

† $P < .05$.

‡ $P < .01$.

tion. Frequent supplementation was encouraged at St Vincent's nursery (3100 m) to prevent dehydration at the higher altitude. Several studies have suggested that there is a relationship between energy or fluid intake and neonatal jaundice.¹⁰⁻¹² The possibility that the effect of altitude on bilirubin levels was masked by greater energy or fluid intake in breast-fed infants at 3100 m relative to 1600 m is supported by the greater proportion of breast-fed infants who received supplements and the higher frequency of supplementation at 3100 m vs 1600 m, but refuted by the lower frequency of breast-feeding in breast-fed infants at 3100 m vs 1600 m (Table 2). Conclusions are limited by small sample sizes and the lack of data on fluid and energy intake in breast-fed infants.

One difference between samples that could not be controlled was the administration of supplemental O₂ to all infants at 3100 m. However, there was no correlation between bilirubin level and the length of time the infant was receiving supplemental O₂ ($r = .06$; $P = .75$). Because barometric pressure is lower at 3100 m, the inspired PO₂ with 24% O₂ at 3100 m was the same as that with room air at 1600 m.

Elevated serum bilirubin values in cord blood samples at 3100 m vs 1600 m suggested that the mechanisms responsible for the altitude-associated neonatal hyperbilirubinemia began before birth. We considered the possibility that increased bilirubin values observed at the higher altitude were a result of decreased intrauterine PO₂, leading to increased red blood cell production and in turn increased bilirubin formation. Increased red blood cell production at high altitude has been interpreted as a compensatory response acting to increase O₂ capacity and help defend arterial O₂ content.¹³ The higher hematocrit values at day 3 at 3100 m are in agreement with previous studies that suggest the possibility of increased red blood cell volume in the newborn at high altitude.¹⁴ Although higher hematocrit values at day 3 at 3100 m may have resulted from insensible fluid loss, no evidence of dehydration at the higher altitude was found when infants at 3100 m and 1600 m were compared for percent of weight gain by day 7 (Table 2). The elevated

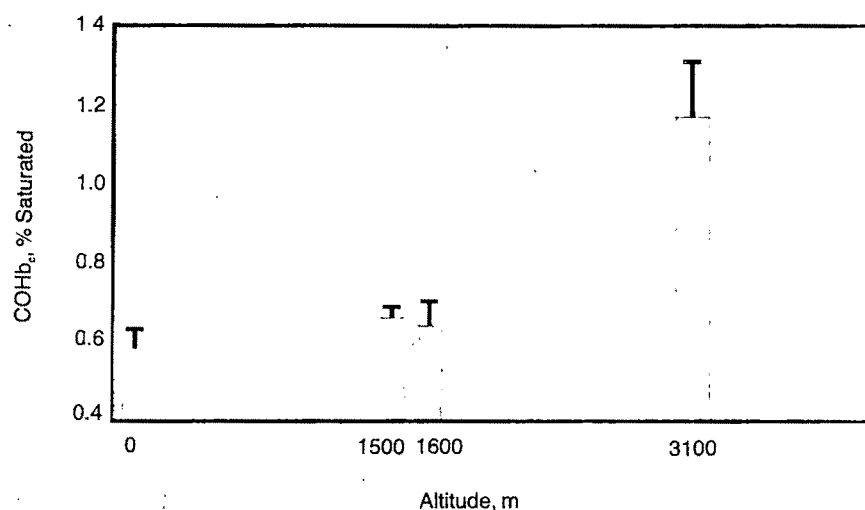


Fig 3.—Mean (\pm SEM) carboxyhemoglobin values corrected for ambient air carbon monoxide (COHb_c) for newborns at sea level ($n = 22$), 1500 m ($n = 17$), 1600 m ($n = 8$), and 3100 m ($n = 17$).

erythropoietin levels in the high-altitude sample are consistent with the possibility that higher hematocrit values at 3100 m reflected increased red blood cell production possibly secondary to fetal or neonatal hypoxemia.^{15,16} Such an interpretation is limited by reports that increased cord blood erythropoietin level may be an acute response to the stress of labor and delivery rather than an index of the stimulus to red blood cell production in utero.^{17,18} The small number of deliveries without labor at 1600 m and 3100 m precluded comparison of erythropoietin levels in the absence of confounding effects of labor.

The most direct evidence for increased bilirubin production at high altitude was provided by increased carboxyhemoglobin levels in the samples at 3100 m. Carbon monoxide is produced as a by-product of heme catabolism in equimolar amounts with bilirubin,¹⁹ and measurement of carboxyhemoglobin has been shown to provide reliable estimates of endogenously produced carbon monoxide and bilirubin production.^{8,20,21} Supportive evidence for greater bilirubin production at higher altitude was provided by values for mean percent of saturation carboxyhemoglobin corrected for ambient air, on newborns at sea level ($0.58\% \pm 0.04\%$; $n = 22$) and at 1500 m ($0.66\% \pm 0.02\%$; $n = 17$) (Fig 3). Samples were analyzed for carboxyhemoglobin in the same laboratory as those obtained at 1600 m and 3100 m.

The association between endogenous carbon monoxide production and car-

boxyhemoglobin is dependent on certain assumptions. These include lack of variance in inspired air carbon monoxide content, diffusing capacity, alveolar ventilation, and oxygen tension.²¹ Variation in inspired carbon monoxide was controlled for by correcting for ambient carbon monoxide. Variation in diffusing capacity (perfusion mismatching or physiologic shunting) would not be expected to have influenced study results to the extent that subjects in both samples were healthy term newborns. With regard to alveolar ventilation, previous studies have suggested levels of endogenous carbon monoxide production, and therefore bilirubin production, are underestimated by measured carboxyhemoglobin values on infants with increased alveolar ventilation.⁸ We did not measure ventilation in the present study, but alveolar ventilation is typically increased at high altitude.²² To the extent that infants at 3100 m exhibited increased alveolar ventilation relative to infants at 1600 m, measured values of carboxyhemoglobin would have underestimated the true values of bilirubin production, in which case differences between altitudes would have been even greater than reported. Carboxyhemoglobin levels are also affected by O₂ tension; higher values at 3100 m might be predicted simply as a result of the reduced competition for hemoglobin binding at the higher altitude.²¹ However, if estimates of arterial O₂ tension at 3100 m (C.L., M.B., unpublished data, 1986) are compared with sea level val-

ues,^{23,24} the expected increase in carboxyhemoglobin levels at 3100 m would only be 0.13%. Thus, reduced competition for hemoglobin binding cannot account for the almost twofold increase in carboxyhemoglobin levels observed in infants at 3100 m compared with that in infants at sea level (Fig 3).

The second major source of elevated bilirubin levels in newborns is decreased capacity for clearance. Decreased capacity can result from impaired hepatic function as well as from incomplete degradation and increased enterohepatic circulation of bilirubin. The effects of hypoxemia on hepatic function, including impaired bilirubin conjugation, have been demonstrated in adults, animal models, and tissue culture.²⁵⁻²⁹

Few tests are available for measuring hepatic function or enterohepatic circulation that can be performed on healthy newborns. To the extent that time and occurrence of first bowel movement provide an index of enterohepatic circulation, similar findings for these mea-

sures at 1600 m and 3100 m did not support increased enterohepatic circulation at high altitude. Although decreased conjugating capacity may be responsible for the lower levels of conjugated bilirubin among infants at 3100 m compared with 1600 m (Table 1), no conclusions can be drawn because total assay variability at this level of measurement is high (SD, 3 $\mu\text{mol/L}$; 8.6% coefficient of variation).

Decreased capacity for clearance has been implicated as the mechanism responsible for the higher peak values and sustained elevation of bilirubin levels typically exhibited by breast-fed vs formula-fed infants.³⁰⁻³² A study by Meyers et al³³ suggested that the higher bilirubin levels observed for breast-fed vs formula-fed infants were not attributable to increased bilirubin production. Although the higher carboxyhemoglobin, erythropoietin, and hematocrit values found for infants at 3100 m relative to 1600 m are consistent with increased bilirubin production at the higher altitude, we cannot exclude the possibility

that decreased capacity for clearance may have contributed to the sustained elevation of bilirubin levels among formula-fed infants at 3100 m vs 1600 m (Fig 2).

The question of whether bilirubin values above 205 $\mu\text{mol/L}$ observed at high altitude are benign or toxic remains to be investigated. Such studies are important for determining when laboratory investigation and therapeutic intervention are appropriate at high altitude as well as for understanding the complex phenomenon of neonatal hyperbilirubinemia.

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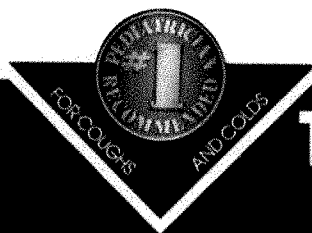
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... on the consumer promotion of infant formula.

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On June 1, the President of the American Academy of Pediatrics sent a letter to all Fellows of the Academy reaffirming its stance against consumer advertising, and expressing concern that other formula companies might follow Nestlé/Carnation.

This concern was justified. On June 15, it was announced at a press conference that Mead Johnson/Bristol-Myers will be producing an infant formula to be sold and marketed under the Gerber label. Part of the program is a multimillion-dollar budget for advertising the formula directly to mothers via TV and print.

Speaking at the press conference, Gerber Products Division President Robert L. Johnston, Jr., said that Gerber was entering the market because it had, "identified significant changes in usage that convinced us the timing was right...."

"First," he said, "there is a rapid decline in breast-feeding after mothers leave the hospital." And, "... parent decision regarding baby formula brand selection has grown...."

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Richard W. Gast

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Twice-Daily Therapy for Strep?

Sir.—I read with interest the article by Gerber et al¹ in the February 1989 issue of *AJDC*. I was especially interested in his final paragraph. In his conclusion he states that his findings support other recommendations, specifically those of the American Heart Association (AHA), that oral penicillin V potassium can be given in two or three divided doses for 10 days for the treatment of group A streptococcal pharyngitis. I referred to the article cited and found that in fact they do not list twice-daily therapy as an acceptable treatment to prevent rheumatic heart disease.²

For those of us in private practice, it would certainly help to have this issue clarified. Does the AHA approve of twice-daily therapy with penicillin V, or any medication other than a salt of erythromycin, as adequate treatment for group A streptococcal pharyngitis?

ELLIS C. GILL, MD
1500 W 38th St
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Austin, TX 78731

1. Gerber MA, Randolph MF, DeMeo K, Feder HM Jr, Kaplan EL. Failure of once-daily penicillin V therapy for streptococcal pharyngitis. *AJDC*. 1989;143:153-155.

2. Dajani AS, Bisno AL, Chung KJ, et al. Prevention of rheumatic fever: a statement of health professionals by the Committee on Rheumatic Fever, Infective Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young. *Circulation*. 1988;78:1082-1086.

In Reply.—In the conclusion of our article,¹ we attempted to make a distinction between our recommendations and those of the AHA. As Dr Gill has correctly observed, the AHA does not list twice-daily penicillin therapy as an acceptable regimen for the treatment of streptococcal pharyngitis.² However, based on our findings³ and those of several other investigators,⁴⁻⁶ we believe that twice-

daily penicillin V therapy is an effective regimen. The Committee on Infectious Diseases of the American Academy of Pediatrics also notes that "with good compliance, two doses of oral penicillin totaling 800,000 U (500 mg) daily have been reported to be effective."⁹

MICHAEL A. GERBER, MD
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1. Gerber MA, Randolph MF, DeMeo K, Feder HM Jr, Kaplan EL. Failure of once-daily penicillin V therapy for streptococcal pharyngitis. *AJDC*. 1989;143:153-155.

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Falls From Pickup Trucks During Childhood

Sir.—Infants and children who are ejected or who fall out of the rear beds

of pickup trucks present a significant but underreported health care issue. Most legislation dealing with child restraint or seat belts issues do not adequately address this problem. We present two cases of children ejected from the rear bed of a pickup truck.

Patient Reports.—PATIENT 1.—A 6-year-old right-handed Navajo boy fell from the back of a pickup truck that was traveling approximately 25 mph over a bumpy rural road. The child struck the frontal portion of his head and experienced a loss of consciousness for a few minutes. After initial evaluation and stabilization, he was transported to our institution. His vital signs on arrival included a heart rate of 70 beats per minute, a blood pressure of 120/65 mm Hg, and a respiratory rate of 20 breaths per minute. Neurologically, he had a Glasgow Coma Score of 9, disconjugate Doll's eyes, right-sided sixth-nerve palsy, and generalized hyperreflexia.

Computed tomography of the brain revealed a small subdural hematoma in the right frontoparietal region with effacement of the right lateral ventricle and a nondepressed right frontal fracture. The patient sustained multiple abrasions. He did not require intracranial pressure monitoring or surgical removal of the subdural hematoma. His condition improved, and he was discharged after 5 days in the hospital with a mild sixth-nerve palsy.

PATIENT 2.—The second patient was a 2-year-old Navajo girl who fell from the back of a slow-moving pickup truck traveling over a rural road. She was initially evaluated and stabilized at another institution, and was noted to have a 7-mm left temporal laceration. Initially, she was crying, combative, and moved all of her extremities. She then became lethargic and unresponsive, and was noted to have jerking eye movements to the right, twitching of her upper extremities, and decreased respirations. The child was endotracheally intubated, given intravenous phenytoin sodium and phenobarbital sodium, and transported to our institution.

On arrival, she was able to withdraw all extremities and open her eyes spontaneously. Computed tomography of her brain revealed a cephalohematoma. It was believed that she had a posttraumatic seizure with secondary respiratory compromise.

he was extubated the next day and had a neurological examination with grossly normal results. She was transferred back to the referring hospital on the second day following the accident.

Comment.—These two patients illustrate the larger number of children treated at our institution with injuries secondary to this mechanism. There is irrefutable evidence that unrestrained children involved in motor vehicle accidents experience higher morbidity and mortality rates than restrained children.^{1,2} This group of children represents the extreme of unrestrained passengers.

Patients 1 and 2 had modified Injury Severity Scores of 18 and 9, respectively. While scores of less than 25 are generally indicative of survival with minimal disability, newer evidence contradicts this. Proportionally more children with head injuries tend to have diffuse rather than focal brain lesions. Children with both "mild" focal and especially diffuse brain injuries often suffer from long-term neuropsychological sequelae.³

Children can be frequently seen riding in the back of pickup trucks where they can easily be ejected during rapid deceleration, fall out during "horseplay" or decreased vigilance, or be injured by road debris. The public and our legislators must be educated. Pediatricians can make this a part of their child restraint and safety education efforts.

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Acute Suppurative Adenoiditis

Sir.—A case of isolated adenoiditis prompted a search of the literature for the condition. The results of the search were startling due to the virtual absence of characterization of what

should be a distinctive, and not unusual, clinical entity.

Patient Report.—A previously healthy 9-year-old girl presented with fever, rhinorrhea, pharyngeal pain, and hyponasal speech of 2 days' duration. She reportedly had had a tonsillectomy and adenoidectomy 3 years earlier for recurrent adenotonsillitis. Abnormalities on physical examination were limited to fever (temperature, 40°C), serous rhinorrhea that prompted nearly constant sniffing, total occlusion of the posterior nasal airway, and an exudative fullness just visible in the superior pharynx behind the uvula. Mild posterior cervical adenopathy was also present. A lateral soft-tissue roentgenogram of the head and neck was obtained (Figure). The posterosuperior location and contour of the nasopharyngeal mass seen on the roentgenogram suggested adenoid hypertrophy. Flexible fiberoptic nasopharyngoscopy revealed exudative hypertrophic adenoid tissue filling the nasopharynx and extending into the oropharynx. The patient was treated with penicillin G sodium and showed prompt defervescence with improvement of her nasal obstructive symptoms. Two months later she underwent a thorough secondary adenoidectomy for persistent nasal obstruction. Histologic analysis of the adenoid tissue revealed reactive follicular hyperplasia.

Comment.—Acute suppurative adenoiditis commonly occurs in association with acute tonsillitis.¹⁻⁴ However, adenoiditis existing independently of tonsillitis has only rarely been mentioned in the literature.^{3,5} Isolated adenoiditis occurs either in the presence of normal-appearing tonsils or as in this case when the tonsils have been previously removed. Adenoiditis and obstructive adenoid hypertrophy do not occur following an adenoidectomy unless the adenoid tissue has been incompletely excised.

A nasopharyngeal mass in the setting of an acute illness with fever and nasal obstruction suggests acute suppurative adenoiditis. The differential diagnosis of other nasopharyngeal masses includes nasopharyngeal angiofibroma (usually male patients), Thornwaldt's cyst, teratoma, antrochoanal polyp, nasopharyngeal carcinoma, malignant lymphoma, and rhabdomyosarcoma.

The bacterial pathogens are not well established in isolated cases of adenoiditis due to the infrequent recognition and reporting of this condition. Initial therapy with antibiotics appropriate for the known pathogens of combined adenotonsillitis can be expected to relieve the symptoms of isolated adenoiditis. These organisms include group A β -hemolytic strepto-



Lateral soft tissue of the neck revealing soft-tissue mass filling the nasopharynx.

cocci, other streptococci, *Haemophilus influenzae*, *Branhamella catarrhalis*, *Corynebacterium* species, and various anaerobic organisms.⁴ Persistent evidence of nasal obstruction after the resolution of acute symptoms indicates the need to consider a trial of antibiotic therapy with action against organisms producing β -lactamase or adenoidectomy. Flexible fiberoptic nasopharyngoscopy is useful for initial evaluation and follow-up.

We encourage reports of similar cases to characterize the clinical spectrum of this disease.

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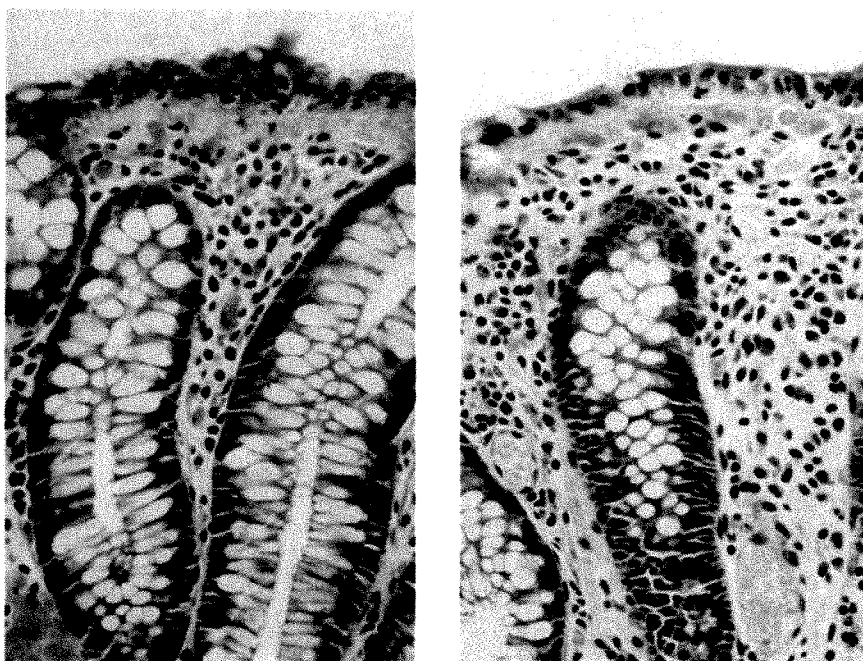
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Collagenous Colitis in a Child

Sir.—To my knowledge, this instance of collagenous colitis in a 7-year-old boy is the first to be documented in a child. This condition is of unknown etiology and, in this case, appeared to respond to



Stained sections from a rectal biopsy specimen showing the normal surface epithelium, the deposition of collagen as a band beneath the basement membrane, and the sparse chronic inflammatory infiltrate within the lamina propria (hematoxylin-eosin, original magnification $\times 140$ [left] and $\times 320$ [right]).

sulfasalazine therapy. Since the original description by Lindstrom¹ in 1976 of the clinicopathologic syndrome that was labeled *collagenous colitis*, about 50 patients^{2,3} with this condition have been described, all adults.

Patient Report.—A 7-year-old boy had complained of large-volume watery diarrhea for several months; there were up to 10 bowel movements per day. Fasting and/or milk abstinence failed to improve the diarrhea. The feces contained no mucus or blood, and no parasites, ova, or pathogenic bacteria were isolated. Results of fecal occult blood studies were negative, and there was no steatorrhea on fecal fat measurements over a 3-day period. Fecal microscopy showed no undigested food. Results of tests for mucoviscidiosis were negative.

Sigmoidoscopy showed a slightly congested mucosa with no ulceration. On barium follow-through and enema studies some colonic dilatation was identified, but no other abnormality was demonstrable. Serum electrolyte levels and hematologic indexes were also within normal limits; no eosinophilia was present. The erythrocyte sedimentation rate was 30 mm within the first hour.

The rectal biopsy specimen showed no ulceration or active inflammation. The mucosa was of normal thickness with a well-maintained glandular architecture and no edema. A continuous, thick, eosinophilic band of collagenous fibrous tissue between 20 and 25 μm wide was readily identifiable between the surface epithelial lining and the lamina propria. This was stainable with both trich-

rome (for type I collagen [Figure, left]) and reticulin silver (for type III collagen [Figure, right]). Staining for amyloid was negative. The glandular tissue was not atrophic, and the goblet-cell content of the crypts was normal. There was a slight lymphoplasmacytic infiltrate within the lamina propria, but no excess of intraepithelial lymphocytes was seen. No cryptitis was seen in numerous serial sections, and there was no vasculopathy.

The child was treated with sulfasalazine, and over a period of a few months he showed some symptomatic improvement. He did not undergo a repeated biopsy.

Comment.—Collagenous colitis is a histologic diagnosis made in patients with chronic abdominal pain and watery diarrhea in the absence of small-intestinal malabsorption and inflammatory bowel diseases. The findings on proctoscopy and sigmoidoscopy are usually minimal and entirely nonspecific, with no impressive finding that could account for the diarrheal illness. These patients may have up to 20 bowel movements per day, and a large fecal volume of up to 4 L/d may be present. Some loss of weight usually accompanies the condition.

Initial presentation is more often in the sixth or seventh decade of life, but some cases have also been described in patients in their 20s. It affects women with greater frequency.

Collagenous colitis is only diagnosable on microscopy.^{2,3} The histologic

hallmark is the presence in the colon of a subepithelial condensation measuring 10 to 60 μm , composed of collagen fibers, including both type I and type III collagens and fibronectin; this layer appears to be more pronounced on the right side of the colon, and the rectosigmoid mucosa may only show minimal changes.^{3,4} A sparse infiltrate composed of plasma cells, eosinophils, and mast cells may be seen within the lamina propria, but no active inflammatory changes are seen either on the surface or in the crypts, and there are no alterations in goblet cell counts. The width of the collagen band does not appear to correlate with the severity of symptoms and waxes and wanes in its thickness over the years. This collagenous tissue may be reabsorbed completely, and such cases are accompanied by spontaneous regression; anti-inflammatory therapy, such as with local corticosteroids and sulfasalazine, may be similarly effective in removing the collagen.^{5,6}

The hypothesis for the cause of collagenous colitis is that long-standing, focal, superficial damage to the large bowel mucosa results in secondary local repair with scarring.^{4,7} Indeed, there appears to be a spectrum of abnormalities, ranging from "microscopic colitis" with active inflammation to collagenous colitis with fibrosis.³ Local prostaglandin excess has been proposed as the immediate pathogenetic mediator; jejunal aspirates and feces from patients have elevated levels of prostaglandin E_2 .⁸ The "pericrypt fibroblast sheath" was proposed as the end organ for the action of such prostaglandin excess.⁹

Histologic examination of bowel mucosal specimens taken at colonoscopy shows that the condition is not limited to the rectum but may extend as far as the cecum and is indeed often more pronounced in the right side of the colon. There is no known association with any specific drug treatment or with connective-tissue disease, and no excess of circulating intestinal polypeptides or amines has been demonstrated in these patients. In six patients, nonspecific anomalies of connective tissue were present, and these were associated with inflammatory arthropathies.^{3,10} Autoimmune mechanisms have been implicated because of the well-established female prevalence and the anecdotal association with atrophic gastritis, thyroid disease, chronic hepatitis, and primary biliary cirrhosis. No immunoglobulins, complement, or immune complexes have been identified in relation to the collagen band.^{6,8}

Subepithelial deposition of collagen is known to occur also in the small bowel in the condition variously termed *refractory sprue* or *collagenous enteritis*,^{11,12} and, indeed, the nomenclature for this disorder was derived from the small-intestinal counterpart. Antigenic hypersensitivity to dietary proteins other than gluten has been suggested as a cause for small-bowel mucosal fibrosis: milk and soya proteins in infants; and maize, egg, and chicken in adults¹² have been implicated. No such dietary association has been shown in collagenous colitis.

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Computed Tomography in the Diagnosis of Osteoid Osteoma in Infancy

Sir.—Osteoid osteoma is a benign bone tumor that principally affects men in

the second decade of life. The clinical manifestations include a characteristic pain with nocturnal exacerbations that recedes or disappears after taking aspirin. In addition, muscular atrophy in the affected extremity and functional impairment are noted. If the tumor is located in the vertebrae, scoliosis can result. The most frequent locations are the femur, tibia, vertebrae, and humerus. A preliminary diagnosis can be made clinically, but confirmation is made by the visualization of the pathognomonic bone lesion, which is the "nidus" surrounded by an area of sclerosis. After surgical treatment, pathological study can confirm the diagnosis by examination of biopsy specimens.

We present a series of patients with osteoid osteoma in whom computed tomography assisted in diagnosis of the lesions.

Patient Reports.—Six children ranging in age from 3 years 5 months to 12 years 6 months were studied and included four boys and two girls with diverse localizations of osteoid osteoma. The clinical symptoms were manifested for a mean of 11 months and consisted of pain with nocturnal paroxysms that improved after administration of aspirin. One patient with osteoid osteoma in the spinal column had scoliosis. In those in whom the osteoma was located in the extremities, muscular atrophy and functional impairment were also observed. The roentgenographic study only identified the specific bone lesion in half of the patients, a characteristic nidus, as well as the perilesional sclerotic bone reaction. All of the patients were treated surgically. The postoperative course was satisfactory for all patients, and the diagnosis of osteoid osteoma was confirmed by pathologic examination.

Comment.—Although the diagnosis of osteoid osteoma can be suspected by the clinical signs and symptoms, it is not unusual that it takes months or years to confirm. The fact that the pain is exacerbated at night and improved with aspirin administration is suggestive of the diagnosis but not specific enough. Due to its rarity in children, it is frequent that the pediatrician does not think of this lesion, above all because the general state of the patient is good and fever or local inflammation is not usually present.¹

The traditional diagnostic test is roentgenography of the affected bone. In the majority of cases, a radiotransparent lesion less than 2 cm in diameter is seen. Its form is oval or round, surrounded by a zone of bone condensation due to reactional hyperostosis.

In other patients, as with our series, a nidus is not visible; therefore computed tomography (CT) of the affected area is indicated.^{2,3} In all of our patients in whom CT was performed, it was possible to identify the nidus and measure its size, which permits differential diagnosis from osteoblastoma. On the other hand, CT also allows the visualization of bone condensation surrounding the nidus, as well as the local muscular atrophy produced by inactivity.

From our results, we conclude that CT is the preferential technique for the diagnosis of osteoid osteomas.

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Clear Heads and Bayesian Tales: Predictive Value and the Coin Toss?

Sir.—Drs Halperin and Doyle, in their response to a recent letter,¹ made an assertion that deserves clarification. They stated that "... diagnosing ITP [idiopathic thrombocytopenic purpura] on the basis of a positive serologic test would be as accurate as flipping a coin," given a positive predictive value of approximately 50%. The statement is accurate in this context, since they were referring to data gathered on a population of patients' sera that had a prevalence of ITP of approximately 50%.² In general, however, using a coin flip as a screening test does not produce a fixed positive predictive value of 50%. Instead, it produces a positive predictive value

equal to the *prevalence* of the disease in the population tested.

The distinction is important. If we choose a disease, for example, with a 5% prevalence, then a coin flip will give a positive predictive value of 5%. If, however, another screening test for that disease is found to have a positive predictive value of 50% in that same population, then the screening test is considerably better than a coin flip.

In this example, a patient with a positive test result has a 10 times greater chance of having the disease in question than does a patient with a positive coin flip. Given a disease that is serious and uncommon, and an intervention that is safe, effective, and inexpensive, we might rationally choose to use such a hypothetical test, despite a "rather low positive predictive value."

The point is this: don't automatically disparage a test with a positive predictive value of 50%. When the disease has a low prevalence, such a test is considerably better than a coin flip.

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In Reply.—Dr Mauro's remarks would be very pertinent if we had suggested in our reply that platelet antibodies should be detected as part of a screening program of ITP in the *general population*. This is not so, however. Such a screening test would be unjustifiable, not only because of its immense costs, but mainly because it would offer no therapeutic or preventive advantage to the patients detected in this manner, as compared with those whose thrombocytopenia has been discovered, as is usually the case, on clinical grounds.

Thus, the controversy regarding the utility of platelet antibody testing is limited to the population of patients with thrombocytopenia and cannot be extrapolated to the general population.

In this setting, our statement on "coin flipping" remains correct. Platelet antibody testing has a positive predictive value for ITP of 50%. In

other words, the probability for a patient with thrombocytopenia of having ITP if the test is positive is only one in two. This is as accurate as flipping a coin.

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In Reply.—Dr Mauro has pointed out a very interesting aspect of the algebra of calculating positive predictive values or PV+.

PV+ is the probability that this subject has the disease tested for (D+) given that the test for the disease is positive (T+). PV+ can be written as $\text{prob}(D+/T+) = \text{the probability of the disease given a positive test}$.

This is a classic Bayes' formula issue and a subtle one that I have not seen discussed anywhere in my reading. For the record, I will go through the algebra in case someone challenges Dr Mauro's assertions.

$$PV+ = \frac{\text{Prev} \times \text{pr}(T+/D+)}{[\text{Prev} \times \text{pr}(T+/D+)] + [(1 - \text{Prev}) \times \text{pr}(T+/D-)]}$$

If you flip a coin instead of performing a test, you will get $\text{pr}(T+/D+) = 0.50$; that is, the probability of a positive test T+ is the probability of, say, "heads."

Also, the probability of a positive test among subjects without the disease, $\text{pr}(T+/D-)$, will also be .50.

Putting these probabilities into the equation, we get the following:

$$PV+ = \frac{\text{Prev} \times .50}{[\text{Prev} \times .50] + [(1 - \text{Prev}) \times .50]}$$

The .50s cancel out, leaving the following:

$$PV+ = \frac{\text{Prev}}{(\text{Prev}) + (1 - \text{Prev})} = \frac{\text{Prev}}{1} = \text{Prevalence}$$

This may seem needlessly esoteric, but to readers who do not think often about Bayes, PV+, or prevalence, the letter may not be intuitively obvious.

An added benefit of the letter is that it reminds us all that PV+ (the predictive value of any test) is always related to the prevalence of the disorder in the population being subjected to the test. This is why a test that performs very well in a clinic that has a high prevalence of a disease may perform poorly as a screening test in

a population with low prevalence of the disease.

For those who view these matters in a less algebraic way, the situation could be looked at differently. The test users apply a test to a population that presents itself to the clinic, hospital, or bootcamp where the test is employed. The disease of interest occurs in the population in some prevalence (PREV).

A coin flip is one way to select half of any group of subjects from the presenting population. If one were to view a flip of "heads" as a "positive test for D" this would result in half of the subjects being called positive for D. What proportion of these would actually have the disease? The same proportion as in the source population, because the coin flip has simply selected a random half of the subjects who are tested.

The proportion of subjects with D in the source population is called the PREV. The proportion with D in the "positives" will be the same (ie, equal to PREV).

In the half who got "tails" and were judged to be "negative" for D, the proportion with the disease would also be the same as in the source (ie, the PREV). This means that the proportion of false negatives also equals the PREV.

Even more general, if one selects any subset of subjects from the source population by any kind of random device (eg, a table of random numbers), that subset will have D in nearly the same proportion as the source population, PREV. The random device will yield PV+ that is equal to the PREV.

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Priapism Following Testosterone Therapy for Delayed Puberty

Sir.—The article by Kaplowitz¹ in the January 1989 issue of *AJDC* again underscores the usefulness of testosterone as an agent for the diagnosis and treatment of delayed puberty. The safety of this therapy is implied in this and other articles discussing this treatment modality.¹⁻³ There is a statement in Kaplowitz's article, similar to that in other articles written on this subject: "Although more frequent erections were noted, this was not felt

to be excessive in any patient." While such a statement appears true for the majority, it is important to note that prolonged painful erections do occur on occasion during such testosterone therapy. We have recently observed three patients who developed prolonged erections during testosterone therapy, one resulting in clinical priapism.

Patient Reports.—PATIENT 1.—A 14-year-7-month-old boy with Tanner stage I sexual development and a growth rate of 3.2 cm/y during the 18 months prior to testosterone therapy received a single 200-mg injection of testosterone enanthate, as the first of four injections. Five days after injection, the patient developed a prolonged nocturnal erection that continued for 5 to 6 hours while at school. Because of embarrassment, he did not tell anyone about his prolonged painful erection until that afternoon when his parents returned home. He was taken to the emergency department at least 8 hours after the inception of his erection and did not respond to amyl nitrite therapy. Our pediatric urologist diagnosed clinical priapism and recommended percutaneous penile irrigation with heparinized saline to remove clotted blood. The patient responded well to the irrigation, but 1 year later, despite entering puberty, he reported no subsequent erections. Clotting studies revealed no abnormalities. A history of some manipulation of the erected penis was elicited as the only

"risk factor" for prolonged erection.

PATIENT 2.—A 14-year-5-month-old boy was treated with testosterone enanthate, 100 mg intramuscularly, as the first of four doses. Following the initial dose, the patient developed a prolonged erection lasting 3 hours. As the patient had been warned to seek medical attention if he had an erection for more than 1 hour, he was taken to the emergency department where he responded to amyl nitrite therapy. The patient had no problems with the next three testosterone doses and has had the expected pubertal response.

PATIENT 3.—A 13-year-9-month-old boy was treated with testosterone enanthate, 100 mg intramuscularly, as the first of four doses. Following this initial injection, he developed a prolonged erection lasting for greater than 1 hour. The patient had been warned to seek medical attention for prolonged erections and thus was seen in the emergency department 2 hours after onset of the prolonged erection. He responded to amyl nitrite therapy. He had no problems with the next three doses and has had the expected pubertal response.

Comment.—Certainly, clinical priapism associated with testosterone therapy is an unusual complication of testosterone therapy for delayed puberty. One isolated case of priapism developing after testosterone injection does not establish a causal connection. Our patient 1 may have had idiopathic priapism, accentuated by the testosterone administration and/

or manual stimulation. However, our experience underscores the need to alert patients and their parents that prolonged erections may occur during testosterone therapy, especially following the initial injection. Prompt evaluation and management of such erections is imperative. The erections generally abate following a cold shower or after inhaling amyl nitrite; however, left untreated, they may result in clinical priapism.

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Inside the new NASALCROM unit is the proven formula patients rely on for relief of sneezing, itching, runny nose, and congestion.^{1,2} NASALCROM provides protection from the first dose¹ and symptom relief within days.² And it works without the annoying side effects typical of other first-line allergic rhinitis medications.^{3,4}

Nonsedating NASAL SOLUTION, 40 mg/mL
NASALCROM®
(cromolyn sodium/FISONS)

**IN THE NEW FULLY-ASSEMBLED UNITS
(26 mL AND 13 mL)**

Please see adjacent page for Brief Summary of Full Prescribing Information.



NASAL SOLUTION, 40 mg/mL

NASALCROM[®]

(cromolyn sodium nasal solution, USP)

Brief Summary

DESCRIPTION: Each milliliter of NASALCROM[®] Nasal Solution (cromolyn sodium nasal solution, USP) contains 40 mg cromolyn sodium in purified water with 0.01% benzalkonium chloride to preserve and 0.01% EDTA (edetate disodium) to stabilize the solution.

INDICATIONS: NASALCROM is indicated for the prevention and treatment of the symptoms of allergic rhinitis.

CONTRAINDICATIONS: NASALCROM is contraindicated in those patients who have shown hypersensitivity to any of the ingredients.

PRECAUTIONS: General: Some patients may experience transient nasal stinging and/or sneezing immediately following instillation of NASALCROM. Except in rare occurrences, these experiences have not caused discontinuation of therapy. In view of the biliary and renal routes of excretion for cromolyn sodium, consideration should be given to decreasing the dosage or discontinuing the administration of the drug in patients with impaired renal or hepatic function.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long term studies in mice (12 months intraperitoneal treatment followed by 6 months observation), hamsters (12 months intraperitoneal treatment followed by 12 months observation), and rats (18 months subcutaneous treatment) showed no neoplastic effect of cromolyn sodium.

No evidence of chromosomal damage or cytotoxicity was obtained in various mutagenesis studies.

No evidence of impaired fertility was shown in laboratory animal reproduction studies.

Pregnancy: Pregnancy Category B. Reproduction studies with cromolyn sodium administered parenterally to pregnant mice, rats, and rabbits in doses up to 338 times the human clinical doses produced no evidence of fetal malformations. Adverse fetal effects (increased resorptions and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Drug Interaction During Pregnancy: Cromolyn sodium and isoproterenol were studied following subcutaneous injections in pregnant mice. Cromolyn sodium alone in doses of 60 to 540 mg/kg (38 to 338 times the human dose) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (90 times the human dose) increased both resorptions and malformations. The addition of cromolyn sodium (338 times the human dose) to isoproterenol (90 times the human dose) appears to have increased the incidence of both resorptions and malformations.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NASALCROM is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.

ADVERSE REACTIONS: The most frequent adverse reactions occurring in the 430 patients included in the clinical trials with NASALCROM were sneezing (1 in 10 patients), nasal stinging (1 in 20), nasal burning (1 in 25), and nasal irritation (1 in 40). Headaches and bad taste were reported in about 1 in 50 patients. Epistaxis, postnasal drip, and rash were reported in less than one percent of the patients. One patient in the clinical trials developed anaphylaxis.

Adverse reactions which have occurred in the use of other cromolyn sodium formulations for inhalation include angioedema, joint pain and swelling, urticaria, cough, and wheezing. Other reactions reported rarely are serum sickness, periarteritic vasculitis, polymyositis, pericarditis, photodermatitis, exfoliative dermatitis, peripheral neuritis, and nephrosis.

CAUTION: Federal law prohibits dispensing without prescription.

References:

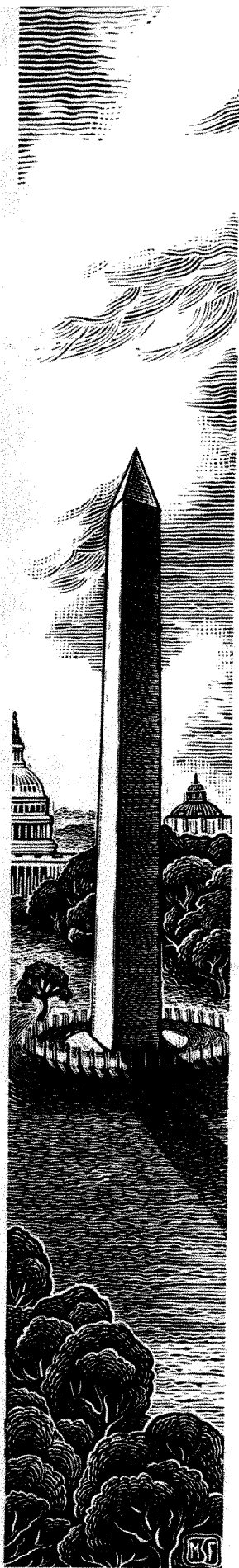
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4. *Physicians' Desk Reference for Nonprescription Drugs[®] (PDR[®])*, ed 9. Oradell, NJ, Medical Economics Co Inc, 1988. Afrin[®] (oxymetazoline hydrochloride), p 685; Chlor-Trimeton[®] (chlorpheniramine maleate), pp 686-687; Actifed[®] (pseudoephedrine hydrochloride, triprolidine hydrochloride), p 530; Sudafed[®] (pseudoephedrine hydrochloride), pp 533-534.

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OVER A CENTURY AGO, a thousand visionary physicians across the nation bestowed a commemorative stone carving to the Washington Monument. This patriotic display symbolized their unrelenting devotion to a new republic founded on freedoms—including the freedom to practice medicine for the best possible health of all its people. *Today your help is needed to restore this symbol of our profession.*



Because the commemorative stone has suffered from severe erosion and defacement, the American Medical Association is launching a campaign to raise money from physicians to restore this symbol of medicine for the National Park Service. Every contribution made to this effort will serve as a statement of each physician's personal affirmation and commitment to health and medicine in America.

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Why Wait for DTP-E-IPV?

In January 1988, a prestigious panel appointed by the Institute of Medicine (IOM) reviewed policy options for vaccination against poliomyelitis.¹ The IOM last reviewed this subject in 1977, at which time it concluded that live, trivalent oral poliovirus vaccine (OPV) was the preferred vaccine but recommended killed, inactivated poliovirus vaccine (IPV) for immunodeficient people and those with immunodeficient family contacts.

See also p 1007.

The new IOM review was prompted in part by licensing of an enhanced potency inactivated polio vaccine (E-IPV). This vaccine, produced in human diploid cells, has a higher antigenic content than does conventional IPV and, therefore, children can be satisfactorily immunized with fewer doses.² A combined diphtheria and tetanus toxoids and pertussis vaccine (DTP)-E-IPV will likely become available within 2 to 5 years.

Other developments prompting the IOM review included the following: (1) the probable interruption of transmission of wild polio virus in the United States; (2) the immunization of an increased proportion of US children (95% of those entering school in 1985-1986); (3) a decreased chance of importation of wild polio due to campaigns in other nations to reduce polio; (4) the development of new technology enabling differentiation of wild vs vaccine-related polio; (5) the recognition that the risk of vaccine-related polio varies with each dose of OPV (for the first dose, the risk is 1:560 000); (6) an increasing number of immunocompromised children and adults due to human immunodeficiency virus infection; and (7) continued immunization litigation.

The IOM concluded that:

No change in the present policy is recommended at this time except that E-IPV

should be substituted for IPV . . . After E-IPV combined with diphtheria-tetanus-pertussis is licensed . . . consideration should be given to a regimen of two or more doses of DTP-E-IPV . . . followed by OPV at 18 months and at entry to elementary school.

The IOM saw the central issue as whether the current small risk of vaccine-associated polio can be reduced further without an adverse impact on poliomyelitis control in the United States. The panel noted that "because E-IPV does not spread to contacts, it would need to achieve and maintain higher levels of direct vaccine-induced immunity to pre- and post-school-age populations." Also, because E-IPV does not produce as high a level of intestinal immunity as OPV, it seems likely that wild polio virus, if imported, would spread more widely.

The panel noted that an ethical difference exists between recommending live vs killed polio vaccine or a mixed live/killed schedule. They observed that vaccine-associated paralytic polio occurs principally among the susceptible children and parents who participate in live vaccination programs. This risk is avoided if a killed vaccine is used and diminished if a killed vaccine is given before a live vaccine is used. The IOM panel stated that:

Most parents concerned only for their child's welfare and informed about the nature of the alternatives would be likely to prefer one of the IPV vaccination strategies. With the current OPV vaccination strategy, cooperating parents and children are asked to bear the risk of vaccine-associated paralysis in order to spread the benefit of immunity to others who fail to have themselves or their children vaccinated.

Recognizing the relatively higher risk of paralytic disease following the first dose of OPV, the panel concluded that a vaccination schedule "in which two or more doses of E-IPV were given prior to OPV would reduce or even eliminate cases of vaccine-associated

paralysis in recipients of OPV and in their contacts." Therefore, the panel recommended a combined E-IPV/OPV schedule to reduce the incidence of vaccine-associated polio but maintain a high degree of intestinal immunity in the population to prevent the spread of wild virus. The panel also noted that if E-IPV was not combined with DTP, additional injections and possibly additional visits would be required to complete the immunization schedule.

The panel expressed concern that a mixed program of E-IPV and OPV "is administratively more complicated and more costly" and stated specifically that the mixed E-IPV/OPV program is not recommended if DTP and E-IPV must be given separately. Only after E-IPV combined with DTP is licensed did the panel suggest consideration be given to a regimen of two or more doses of DTP-E-IPV followed by OPV at age 18 months.

The panel observed that more information is needed about the following questions: (1) Is wild polio virus circulating in the United States? (2) What are the levels of immunity among young adults and preschool children? (3) To what extent does OPV vaccine virus spread to contacts of recipients and induce immunity? (4) What would be the optimal combined E-IPV/OPV vaccine strategy? It is precisely because the answers to these questions are not known that practitioners look to panels of experts for recommendations.

The IOM panel's rationale for a combined schedule is cogent. Many knowledgeable, thoughtful observers are no longer convinced that the "price" of vaccine-associated polio must be paid to protect this nation against wild polio virus. On the other hand, there are not sufficient data to assure such observers that complete reliance on inactivated vaccine would provide comparable protection against com-

munity spread of wild polio virus following its introduction. Therefore, a combined E-IPV/OPV schedule that should lower the number of vaccine-associated cases (albeit not eliminating all of them) while preserving a high incidence of intestinal immunity seems wise. But why wait?

The potential benefits of such a change in vaccine policy may be marginal when viewed from a nationwide or generational perspective. For the patients, families, or physicians involved in each vaccine-associated case, the potential benefit is far from marginal. Why should introduction of a combined E-IPV/OPV schedule await the production of a combined DTP-E-IPV vaccine? Why shouldn't those who wish to lower their risk of vaccine-associated polio *now* opt for a combined IPV/OPV schedule? The IOM panel's concern is, that because such a schedule is more costly and might prove cumbersome, the total number of children successfully immunized might decrease. The panel viewed this as an inappropriate "cost" given the relatively marginal benefit of a combined schedule for vaccine-associated cases.

A combined OPV and IPV schedule in the absence of a combined DTP-E-IPV vaccine will likely cost more. In January 1989, in Seattle, Wash, E-IPV cost approximately \$14 a dose vs \$9.50 a dose for OPV. Also,

a combined E-IPV/OPV schedule would, at this time, require two or three additional subcutaneous injections. Were such a schedule now recommended *exclusively*, there might well be some decrease in the total number of children protected because the prompt availability of increased funds for immunization could not be assured.

No one wishes to advocate different immunization policies for patients immunized in public clinics vs private offices. But postponing a preferred strategy because of cost raises difficult issues. The price of vaccine is affected by the size of the potential market: the price of E-IPV would almost certainly decrease were its use mandated and vaccine for public immunization programs purchased by federal contract, as is OPV. In the absence of such a mandate, the market will likely remain small and the price high. The additional cost of administering two or three subcutaneous injections of E-IPV vs two or three oral doses of OPV is less easily determined, but it is likely to be the major increased cost that needs to be balanced against the benefit of a reduced risk of paralytic disease among vaccinees and their contacts until a combined DTP-E-IPV is available.

The question answered by the IOM and the one implicitly posed by parents to their children's physicians are

subtly different. The IOM was asked: What is now the optimal vaccination policy for control of polio in the *nation*? The parent asks, What is now the optimal way to protect *my child and family* against polio? What if the practitioner is confident the family will persevere despite the need for two or three more shots and a slightly more expensive schedule to reduce their child's risk of vaccine-associated polio from approximately 1 in 560 000 to 1 in 10.5 million? If, in the judgment of the child's physician and parents, the cost and discomfort of a combined E-IPV and OPV schedule is acceptable, it seems the optimal way to immunize an individual child against polio *today*.

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Poliovirus Vaccine Policy

Another Perspective

Throughout the 1950s parents greeted each summer with mounting anxiety as outbreaks of polio were responsible annually for 20 000 to 25 000 cases of paralytic disease. In 1954, the Fran-

See also p 1006.

cis field trial demonstrated the efficacy of inactivated polio virus vaccine (IPV) in the prevention of this dread infection. Beginning in 1955, widespread use of IPV resulted in a marked decline in the annual reported incidence of polio. In

1959, however, there was an incipient upswing in the number of people contracting polio, a significant proportion of whom had previously received three or more injections of IPV. Coupled with the dramatic reports of the success of oral polio virus vaccine (OPV) in Europe and other parts of the world, a shift took place in 1961 in the United States with a transition from the IPV to an OPV program. Soon thereafter, reported cases of paralytic disease due to polioviruses plummeted to levels less than 100 cases per year with the virtual

disappearance of epidemic disease. The last outbreak in our country occurred in 1979 and involved only 10 cases within an Amish population who, for religious reasons, had declined immunization.

Aside from the solitary cases of polio recognized annually as imported from abroad, nearly all the reports now (from two to eight per year) are of OPV vaccine-associated paralytic disease, either in recipients or their contacts.¹ The failure of the imported cases to initiate a cluster of paralytic disease attests to the excellence of our

individual and community immunologic barriers to spread. The focus of the IPV-OPV debate continues to be the diminishing number of vaccine-associated cases (there were two cases in the preliminary report for 1988) as "the price" we pay for national control of polio. Vaccine-associated paralytic disease has been carefully studied, and with modern molecular virologic techniques² it is possible to show that many, if not most, cases result from a mutation of the type III vaccine virus component. A very small proportion of the vaccine-associated cases (<10%) occur among individuals with severe immunodeficiency disorders who are inadvertently fed OPV prior to the diagnosis of their underlying disease. Results of genetic manipulations of the OPV seed strains, especially type III, offer encouragement that a more stable mutant is achievable, ensuring preservation of immunogenicity with loss of potential for reversion to neurovirulence.

Throughout the past several decades, proponents of IPV have pointed to the admirable records of polio elimination in a number of European countries (especially Holland and several of the Scandinavian nations) where IPV alone had been used. In the last 10 years, however, several unsettling events occurred in these nations and elsewhere. In 1978, 110 cases of type I disease occurred in the Netherlands among a population who had refused immunization. In 1984 to 1985, an outbreak of type III paralytic polio in Finland resulted in nine cases of paralytic disease, five of them among individuals who had previously received as many as five doses of IPV. In both outbreaks, there was evidence of widespread dissemination of the "wild" virus by healthy, IPV-immunized schoolchildren. This raised the oft-debated issues of both the individual value of gastrointestinal tract immunity and its barrier as community protection against circulation of virulent virus and outbreaks of paralytic polio. Probably the most cogent example occurred recently in one district (Hadera) of Israel. In 1982, that district chose to discontinue OPV and to adopt the new, enhanced IPV (E-IPV) for its routine immunization schedule.

In the summer and fall of 1988, 12 cases of paralytic disease occurred in Hadera, principally among individuals over 17 years of age. Studies of fecal excretion of schoolchildren revealed widespread dissemination and shedding of the responsible agent, a "wild" type I virus. Although the children themselves were not the victims of paralytic disease, their susceptible gastrointestinal tracts served as the reservoirs and vectors for transmission of the "wild" virus, which was successful in infecting those young adults who had incomplete immunity. In these considerations, it is important to remember that the populations of Finland and Israel total 4.8 and 4.6 million, respectively, so that such numbers extrapolated to a nation of our size could have meant from 450 to 600 cases of paralytic disease.

On two occasions, the Institute of Medicine of the National Academy of Sciences, Washington, DC, has been asked to assemble expert panels to consider polio vaccine immunization policy for the United States. In 1977, such a conference resulted in a recommendation that OPV continue as the primary vaccine for our country and that IPV be available for selected individuals who might be at increased risk for the rare paralytic events of OPV. In 1988, a similar conference was held at the Institute of Medicine and the issues were extensively reexamined. The recommendations were that OPV be maintained as the primary vaccine, but that consideration be given to a combined schedule involving E-IPV to be followed by OPV, once it was possible to combine E-IPV with diphtheria and tetanus toxoids and pertussis (DTP) vaccine. In this way, the childhood immunization schedule could be maintained in its present form with only minor changes that would be unlikely to result in an increased number of child health visits or a diminution of vaccine coverage. Currently, there are vaccines used abroad that combine E-IPV with DTP, but these use the whole-cell pertussis vaccine, which is itself currently under scrutiny in this country and elsewhere. Most vaccine producers are reluctant to move into the mode of combined E-IPV/DTP until a decision

has been made regarding the use of newer acellular pertussis vaccines. The progress of these studies has been reported elsewhere.³

Lengthy debates, both oral and written, have been conducted regarding polio vaccine policies. Recent articles^{4,5} summarize fully the protagonists' views. Dr Marcuse, in a separate editorial in this issue of *AJDC*, suggests that we move ahead now with the E-IPV/OPV combined schedule without the recommendation of the American Academy of Pediatrics or public health groups (such as the Immunization Practices Advisory Committee).

Although Dr Marcuse's suggestion may eventually be similar to recommended policies, there are unanswered questions that expert advisory committees believe should be addressed before any major change is made in our vaccine policy. These relate to the same questions that arose with the outbreaks in Finland and Israel: (1) How important is circulation of the oral vaccine virus in the establishment of immunity among preschoolchildren who do not receive any vaccine? (2) How important is gastrointestinal tract immunity in preventing the circulation of wild polioviruses introduced from nations where endemic disease persists? (More than 1700 cases of suspected paralytic polio were reported in 1988 in Central and South America.⁶) (3) How effective is our health care system in providing immunization for the target population, children under 2 years of age? (Current outbreaks of measles among infants from urban areas who have not been immunized have been studied in Los Angeles, Calif, Houston, Tex, New York, NY, and other areas where such populations are increasing.) Although more than 97% of youngsters entering school have been properly immunized because of entry requirements, the preschool populations in some areas have immunization rates as low as 50%. Until we have established a health care provision system that ensures the immunization of nearly 100% of such youngsters, can we rely on an unfulfilled E-IPV/OPV combined schedule that may leave many such youngsters with neither

humoral nor gastrointestinal tract immunity? Our success in preventing the spread of any of the recent introductions of wild poliovirus in this country has depended on high levels of immunity engendered by the widespread use and circulation of OPV and its establishment of gastrointestinal tract immunity.

Another major concern of a premature adoption in this country of the combined E-IPV/OPV schedule would be the likely establishment of a "two-class" system. Those infants whose care is in private physicians' offices might receive the combined schedule; those in public health clinics would continue with OPV alone. Such a disparity in child health care is contrary

to the spirit of child advocacy embraced by pediatricians. Current estimates reveal that at least 50% of preschool children are immunized in public health clinics. Until the problems of acellular pertussis vaccine have been successfully resolved, until the questions posed by advisory committees regarding the current assets of OPV in the United States have been investigated, and until vaccines can be delivered to all children in the first 2 years of life, a change may be premature.

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In Other AMA Journals

ARCHIVES OF SURGERY

Increased Incidence of Delayed Gastric Emptying in Children With Gastroesophageal Reflux: A Prospective Evaluation

John G. Papaila, MD; David Wilmot, MD; Jay L. Grosfeld, MD; Frederick J. Rescorla, MD; Warren W. West, MD; Dennis W. Vane, MD (*Arch Surg*. 1989;124:933-936)

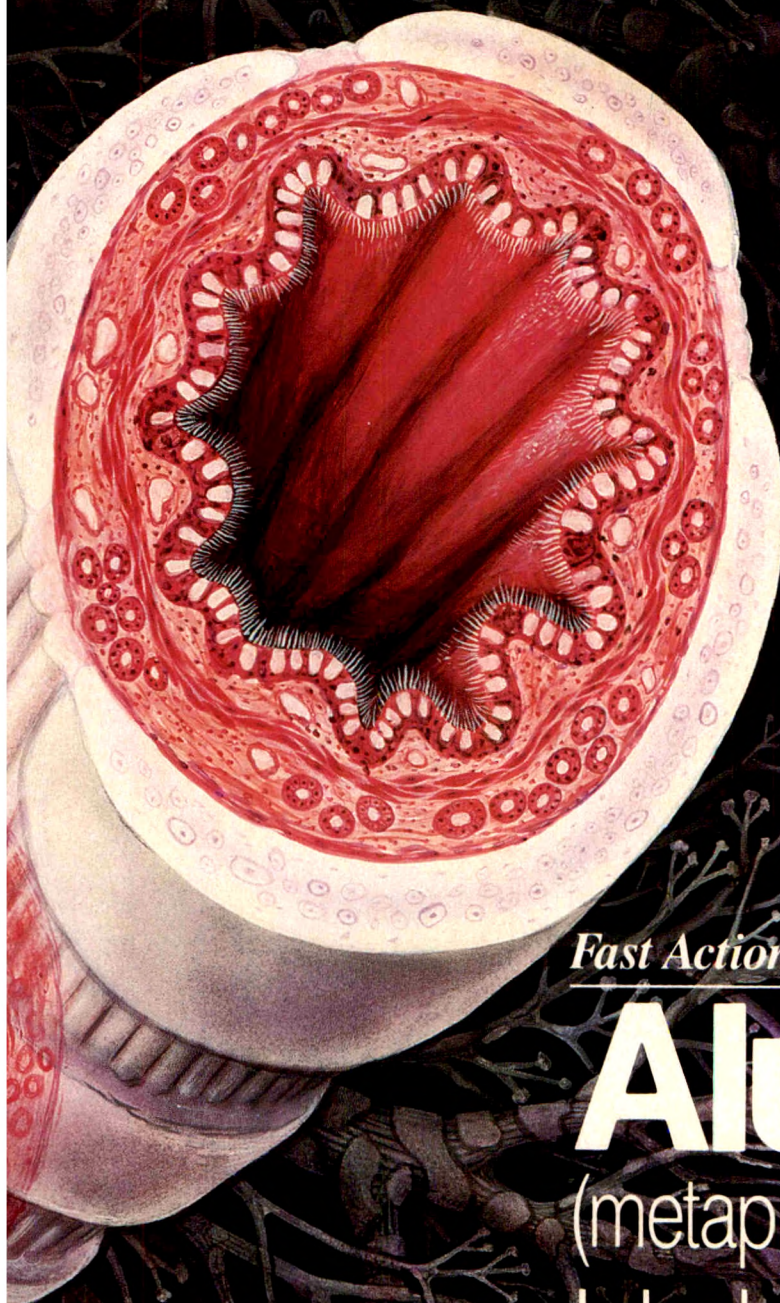
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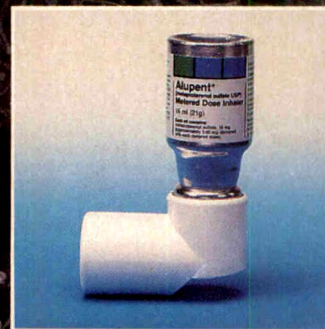
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Please see following page for brief summary of prescribing information

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†15 mg/ml (each metered dose delivers 0.65 mg metaproterenol sulfate)

Brief Summary of Prescribing Information

CONTRAINDICATIONS Use in patients with cardiac arrhythmias associated with tachycardia is contraindicated.

Although rare, immediate hypersensitivity reactions can occur. Therefore Alupent® (metaproterenol sulfate USP) is contraindicated in patients with a history of hypersensitivity to any of its components.

WARNINGS Excessive use of adrenergic aerosols is potentially dangerous. Fatalities have been reported following excessive use of Alupent® (metaproterenol sulfate USP) as with other sympathomimetic inhalation preparations, and the exact cause is unknown. Cardiac arrest was noted in several cases. Paradoxical bronchoconstriction with repeated excessive administration has been reported with sympathomimetic agents. Therefore, it is possible that this phenomenon could occur with Alupent. Patients should be advised to contact their physician in the event that they do not respond to their usual dose of a sympathomimetic amine aerosol.

PRECAUTIONS Because Alupent® (metaproterenol sulfate USP) is a sympathomimetic drug, it should be used with great caution in patients with hypertension, coronary artery disease, congestive heart failure, hyperthyroidism or diabetes, or when there is sensitivity to sympathomimetic amines.

Information for Patients Extreme care must be exercised with respect to the administration of additional sympathomimetic agents. A sufficient interval of time should elapse prior to administration of another sympathomimetic agent.

Carcinogenesis Long-term studies in mice and rats to evaluate the oral carcinogenic potential of metaproterenol sulfate have not been completed. Studies of metaproterenol sulfate have not been conducted to determine mutagenic potential or effect on fertility.

Pregnancy *Teratogenic Effects.* Pregnancy Category C. Alupent has been shown to be teratogenic and embryocidal in rabbits when given orally in doses 620 times the human inhalation dose and 62 times the human oral dose. There are no adequate and well-controlled studies in pregnant women. Alupent should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Oral reproduction studies in mice, rats and rabbits showed no teratogenic or embryocidal effects at 50 mg/kg, corresponding to 310 times the human inhalation dose and 31 times the human oral dose. Teratogenic effects in the rabbit included skeletal abnormalities and hydrocephalus with bone separation.

Nursing Mothers It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Alupent is administered to a nursing woman.

Pediatric Use Consult package insert for age limit.

ADVERSE REACTIONS Adverse reactions are similar to those noted with other sympathomimetic agents. Adverse reactions such as tachycardia, hypertension, palpitations, nervousness, tremor, nausea and vomiting have been reported.

The most frequent adverse reactions to Alupent® (metaproterenol sulfate USP) Inhalation Solution are nervousness and tachycardia which occur in about 1 in 7 patients, tremor which occurs in about 1 in 20 patients and nausea which occurs in about 1 in 50 patients. Less frequent adverse reactions are hypertension, palpitations, vomiting and bad taste which occur in approximately 1 in 300 patients.

HOW SUPPLIED *Inhalation Aerosol:* Each canister of Alupent® (metaproterenol sulfate USP) Inhalation Aerosol contains 225 mg of metaproterenol sulfate as a micronized powder in inert propellants. Alupent Inhalation Aerosol with mouthpiece (15 ml). Alupent Inhalation Aerosol refill (15 ml). Store below 77°F (25°C). Avoid excessive humidity.

Inhalation Solution: Alupent Inhalation Solution is supplied as a 5% solution in bottles of 10 ml or 30 ml with accompanying calibrated dropper.

Store below 77°F (25°C). Protect from light. Do not use the solution if it is brown or has a precipitate. Alupent Inhalation Solution Unit-dose Vial is supplied as a 0.4% or 0.6% clear colorless or nearly colorless solution containing 2.5 ml with 25 vials per box. Store below 77°F (25°C). Protect from light. Do not use the solution if it is brown or has a precipitate.

Syrup: Alupent is available as a cherry-flavored syrup, 10 mg per teaspoonful (5 ml), in 16 fl. oz. bottles. Store below 86°F (30°C). Protect from light.

Tablets: Alupent is supplied in two dosage strengths as scored, round white tablets in bottles of 100. Tablets of 10 mg coded BI/74. Tablets of 20 mg coded BI/72.

Storage for bottles: Store below 86°F (30°C). Protect from light.

Storage for blister samples: Store below 77°F (25°C). Protect from light.

Consult package insert before prescribing.

AL-4268

AL-BPI-1/88



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Recommendations of the Immunization Practices Advisory Committee (ACIP)

General Recommendations on Immunization

THIS REVISION OF the "General Recommendations on Immunization" updates the 1983 statement.¹ Changes or new sections include 1) listing of vaccines available in the United States by type and recommended routes, 2) updated schedules for immunizing infants and children, 3) clarification of the guidelines for spacing administration of immune globulin preparations and different vaccines, 4) an updated table of recommendations for routine immunization of children infected with human immunodeficiency virus, 5) listing of conditions that are often inappropriately considered contraindications to immunization, and 6) addition of information on the National Childhood Vaccine Injury Act of 1986 and the National Vaccine Injury Compensation Program. These recommendations are not comprehensive for each vaccine; Immunization Practices Advisory Committee (ACIP) recommendations on each vaccine should be consulted for more details.

INTRODUCTION

Recommendations for immunizing infants, children, and adults are based on characteristics of immunobiologics, scientific knowledge about the principles of active and passive immunization, and judgments by public health officials and specialists in clinical and preventive medicine. Benefits and risks are associated with the use of all immunobiologics: no vaccine is completely safe or completely effective. Benefits of immunization range from partial to complete protection against the consequences of disease (which range from mild or asymptomatic infection to severe consequences, such as paralysis or death); risks of immunization range from common, trivial, and inconvenient side effects to rare, severe, and life-threatening conditions. Thus, recommendations for immunization practices balance scientific evidence of benefits, costs, and risks to achieve optimal levels of protection against infectious diseases. These rec-

ommendations describe this balance and attempt to minimize the risks by providing specific advice regarding dose, route, and spacing of immunobiologics and delineating situations that warrant precautions or contraindicate their use. They are recommendations for use in the United States because epidemiologic circumstances and vaccines often differ in other countries. Individual circumstances may warrant deviations from these recommendations. The relative balance of benefits and risks can change as diseases are controlled or eradicated. For example, because smallpox has been eradicated throughout the world, the risk of complications associated with smallpox vaccine now exceeds the risk of the disease; consequently, smallpox vaccination of civilians is now indicated only for laboratory workers directly involved with smallpox or closely related orthopox viruses (e.g., monkeypox and vaccinia).

DEFINITIONS

Immunobiologic

Immunobiologics include both antigenic substances, such as vaccines and toxoids, and antibody-containing preparations, including globulins and antitoxins, from human or animal donors. These products are used for active or passive immunization or therapy. Examples include:

Vaccine: A suspension of live (usually attenuated) or inactivated microorganisms (bacteria, viruses, or rickettsiae) or fractions thereof administered to induce immunity and thereby prevent infectious disease. Some vaccines contain highly defined antigens (e.g., the polysaccharide of *Haemophilus influenzae* type b or the surface antigen of hepatitis B); others have antigens that are complex or incompletely defined (e.g., killed *Bordetella pertussis* or live attenuated viruses).

Toxoid: A modified bacterial toxin that has been rendered nontoxic but retains the ability to stimulate the formation of antitoxin.

Immune globulin (IG): A sterile solution containing antibodies from human blood. It is obtained by cold ethanol fractionation of large pools of blood plasma and contains 15%-18% protein. Intended for intramuscular administration, it is primarily indicated for routine maintenance of immunity of certain immunodeficient persons and for passive immunization against measles and hepatitis A. IG does not transmit hepatitis B virus, human immunodeficiency virus (HIV), or other infectious diseases.

Intravenous immune globulin (IGIV): A product derived from blood plasma from a donor pool similar to the IG pool but prepared so it will be suitable for intravenous use. IGIV does not transmit infectious diseases. It is primarily indicated for replacement therapy in antibody-deficiency disorders.

Specific IG: Special preparations obtained from blood plasma from donor pools preselected for a high antibody content against a specific antigen, e.g., hepatitis B immune globulin (HBIG), varicella-zoster immune globulin, rabies immune globulin, and tetanus immune globulin. Like IG and IGIV, these preparations do not transmit infectious diseases.

Antitoxin: A solution of antibodies derived from the serum of animals immunized with specific antigens (e.g., diphtheria antitoxin, botulinum antitoxin) used to achieve passive immunity or for treatment.

Vaccination and Immunization

These terms are often used interchangeably. Vaccination and vaccine derive from vaccinia, the virus once used as smallpox vaccine. Thus, vaccination originally meant inoculation with vaccinia virus to render a person immune to smallpox. Although some persons still prefer that vaccination be restricted to this use, most use it to denote the administration of any vaccine or toxoid.

Immunization is a more inclusive

term denoting the process of inducing or providing immunity artificially by administering an immunobiologic. Immunization can be active or passive.

Active immunization is the production of antibody or other immune responses to the administration of a vaccine or toxoid. Passive immunization means the provision of temporary immunity by the administration of preformed antibodies. Three types of immunobiologics are administered for passive immunization: 1) pooled human IG or IGIV, 2) specific IG preparations, and 3) antitoxins.

Vaccination and immunization are used interchangeably in ACIP statements in reference to active immunization. Regardless of which term is used, administration of an immunobiologic cannot be automatically equated with the development of adequate immunity for a variety of reasons, many of which are discussed below.

IMMUNOBIOLOGICS

The specific nature and content of immunobiologics can differ. When immunobiologics against the same infectious agents are produced by different manufacturers, active and inert ingredients in the various products are not always the same. Practitioners are urged to become familiar with the constituents of the products they use.

Suspending Fluids

These may be sterile water or saline or complex fluids containing small amounts of protein or other constituents derived from the medium or biologic system in which the vaccine is produced (e.g., serum proteins, egg antigens, cell-culture-derived antigens).

Preservatives, Stabilizers, Antibiotics

These components of vaccines, antitoxins, and globulins are used to inhibit or prevent bacterial growth in viral cultures or the final product or to stabilize the antigens or antibodies. Allergic reactions can occur if the recipient is sensitive to one of these additives (e.g., mercurials, phenols, albumin, glycine).

Adjuvants

Many antigens evoke insufficient immunologic responses when given in their natural state. Efforts to enhance immunogenicity include mixing antigens with a variety of substances or adjuvants (e.g., aluminum adjuvants such as aluminum phosphate).

ROUTE, SITE, AND TECHNIQUE OF IMMUNIZATION

Route

Routes of administration are recommended for each immunobiologic. To avoid unnecessary local or systemic effects and/or to ensure optimal efficacy, the practitioner should not deviate from the recommended routes. Vaccines containing adjuvants must be injected deep into the muscle mass; they should not be administered subcutaneously or intradermally because they can cause local irritation, inflammation, granuloma formation, or necrosis. Site Injectable immunobiologics should be administered where there is little likelihood of local, neural, vascular, or tissue injury. Subcutaneous injections are usually administered into the thigh of infants and in the deltoid area of older children and adults. Intradermal injections are generally given on the volar surface of the forearm except for human diploid cell rabies vaccine with which reactions are less severe in the deltoid area. The preferred sites for intramuscular injections are the anterolateral aspect of the upper thigh and the deltoid muscle of the upper arm. In most infants, the anterolateral aspect of the thigh provides the largest muscle mass and is therefore the preferred site. An individual decision must be made for each child based on the volume of the material to be administered and the size of the muscle into which it is to be injected. In adults, the deltoid is recommended for routine intramuscular vaccine administration, particularly for hepatitis B vaccine. The buttock should not be used routinely as a vaccination site for infants, children, or adults because of the risk of injury to the sciatic nerve. In addition, injection into the buttock has been associated with decreased immunogenicity of hepatitis B and rabies vaccines, presumably because of inadvertent subcutaneous injection or injection into deep fat tissue. If the buttock is used when very large volumes are to be injected or multiple doses are necessary (e.g., large doses of IG), the central region should be avoided; only the upper, outer quadrant should be used.

Techniques

Syringes and needles used for injections must be sterile and preferably disposable to minimize the risk of contamination. For an intramuscular injection, the needle and syringe

should be of sufficient length and bore to reach the muscle mass itself and prevent vaccine from seeping into subcutaneous tissue. For children, a 20- or 22-gauge needle 1 to 1-1/2 inches long is recommended. For small infants, a 25-gauge 5/8-inch-long needle may be adequate. For adults, the suggested needle length is 1-1/2 inches. For subcutaneous or intradermal injections, a 25-gauge needle 5/8-3/4 inches long is recommended.

Before the injection is given, the needle is inserted in the site and the syringe plunger pulled back; if blood appears, the needle should be withdrawn and a new site selected. The process should be repeated until no blood appears. A separate needle and syringe should be used for each vaccine injected. Disposable needles and syringes should be discarded into labeled, puncture-proof containers to prevent accidental needlesticks or reuse. If more than one vaccine preparation is administered or if vaccine and IG are administered simultaneously, each should be given at a different site.

DOSAGE

The recommendations on dosages of immunobiologics are derived from theoretical considerations, experimental trials, and clinical experience. Administration of volumes smaller than those recommended, such as split doses or intradermal administration (unless specifically recommended), can result in inadequate protection. Use of larger than the recommended dose can be hazardous because of excessive local or systemic concentrations of antigens.

The ACIP strongly discourages any variation from the recommended volume or number of doses of any vaccine. Some practitioners use smaller, divided, doses of vaccine, thereby reducing the total immunizing dose. Others use multiple smaller doses that together equal a full immunizing dose (e.g., diphtheria and tetanus toxoids and pertussis vaccine (DTP)) in an effort to reduce reactions. However, the serologic response, clinical efficacy, and/or frequency and severity of adverse reactions of such schedules have not been adequately studied.

AGE AT WHICH IMMUNOBIOLOGICS ARE ADMINISTERED

Several factors influence recommendations concerning the age at

which vaccines are administered; they are age-specific risks of disease, age-specific risks of complications, ability of persons of a given age to respond to the vaccine(s), and potential interference with the immune response by passively transferred maternal antibody. In general, vaccines are recommended for the youngest age group at risk whose members are known to develop an acceptable antibody response to vaccination.

SPACING OF IMMUNOBIOLOGICS **Multiple Doses of Same Antigen**

Some products require administration of more than one dose for development of an adequate antibody response. In addition, some products require periodic reinforcement (booster) doses to maintain protection. In recommending the ages and/or intervals for multiple doses, the ACIP takes into account risks from disease and the need to induce or maintain satisfactory protection.

Intervals between doses that are longer than those recommended do not lead to a reduction in final antibody levels. Therefore, it is not necessary to restart an interrupted series of an immunobiologic or to add extra doses.

In contrast, giving doses of a vaccine or toxoid at less than recommended intervals may lessen the antibody response and therefore should be avoided. Doses given at less than recommended intervals should not be counted as part of a primary series.

Some vaccines produce local or systemic symptoms in certain recipients when given too frequently (e.g., Td, DT, and rabies). Such reactions are thought to result from the formation of antigen-antibody complexes. Good recordkeeping, careful patient histories, and adherence to recommended schedules can decrease the incidence of such reactions without sacrificing immunity.

Different Antigens

Experimental evidence and extensive clinical experience have strengthened the scientific basis for giving certain vaccines at the same time. Many of the widely used vaccines can safely and effectively be given simultaneously (i.e., on the same day, not at the same site). This knowledge is particularly helpful when there is imminent exposure to several infectious diseases, preparation for foreign travel, or uncertainty that the person

will return for further doses of vaccine.

1. Simultaneous Administration

In general, inactivated vaccines can be administered simultaneously at separate sites. However, when vaccines commonly associated with local or systemic side effects (e.g., cholera, typhoid, and plague) are given simultaneously, the side effects can be accentuated. Whenever possible, these vaccines should be given on separate occasions.

Simultaneous administration of pneumococcal polysaccharide vaccine and whole-virus influenza vaccine elicits satisfactory antibody responses without increasing the incidence or severity of adverse reactions. Simultaneous administration of the pneumococcal vaccine and split-virus influenza vaccine can also be expected to yield satisfactory results. Influenza vaccine should be administered annually to the target population. In general, simultaneous administration of the most widely used live and inactivated vaccines has not resulted in impaired antibody responses or increased rates of adverse reactions. Administration of combined measles, mumps, and rubella (MMR) vaccine yields results similar to administration of individual measles, mumps, and rubella vaccines at different sites. Therefore, there is no medical basis for giving these vaccines separately for routine immunization instead of the preferred MMR combined vaccine.

There are equivalent antibody responses and no clinically significant increases in the frequency of adverse events when DTP, MMR, and oral polio vaccine (OPV) or inactivated polio vaccine (IPV) are administered either simultaneously at different sites or separately. As a result, routine simultaneous administration of MMR, DTP, and OPV (or IPV) to all children greater than or equal to 15 months who are eligible to receive these vaccines is recommended. Administration of MMR at 15 months followed by DTP and OPV (or IPV) at 18 months remains an acceptable alternative, especially for children with caregivers known to be generally compliant with other health-care recommendations. Data are lacking on concomitant administration of Haemophilus influenzae b conjugate vaccine (HbCV) or Haemophilus influenzae b polysaccharide vaccine (HbPV) and MMR and

OPV vaccine. If the child might not be brought back for future immunizations, the simultaneous administration of all vaccines (including DTP, OPV, MMR, and HbCV or HbPV) appropriate to the age and previous vaccination status of the recipient is recommended. Hepatitis B vaccine given with DTP and OPV or given with yellow fever vaccine is as safe and efficacious as these vaccines administered separately.

The antibody responses of both cholera and yellow fever vaccines are decreased if given simultaneously or within a short time of each other. If possible, cholera and yellow fever vaccinations should be separated by at least 3 weeks. If there are time constraints and both vaccines are necessary, the injections can be given simultaneously or within a 3-week period with the understanding that antibody response may not be optimal. Decisions on the need for yellow fever and cholera immunizations should take into account the amount of protection afforded by the vaccine, the possibility that environmental or hygienic practices may be sufficient to avoid disease exposure, and the existence of vaccination requirements for entry into a country.

2. Nonsimultaneous Administration

Inactivated vaccines do not interfere with the immune response to other inactivated vaccines or to live vaccines except, as noted above, with cholera and yellow fever vaccines. In general, an inactivated vaccine can be given either simultaneously or at any time before or after a different inactivated vaccine or a live vaccine.

There are theoretical concerns that the immune response to one live-virus vaccine might be impaired if given within 30 days of another. Whenever possible, live-virus vaccines not administered on the same day should be given at least 30 days apart.

Live-virus vaccines can interfere with the response to a tuberculin test. Tuberculin testing can be done either on the same day that live-virus vaccines are administered or 4-6 weeks afterwards.

Immune Globulin

If administration of an IG preparation becomes necessary because of imminent exposure to disease, live-virus vaccines can be given simulta-

neously with the IG product, with the recognition that vaccine-induced immunity might be compromised. The vaccine should be administered at a site remote from that chosen for the IG inoculation. Vaccination should be repeated about 3 months later unless serologic testing indicates that specific antibodies have been produced. OPV and yellow fever vaccines are exceptions, however, and are not affected by administration of IG at any time.

Live, attenuated vaccine viruses might not replicate successfully, and antibody response could be diminished when the vaccine is given after IG or specific IG preparations. Whole blood or other antibody-containing blood products can interfere with the antibody response to measles, mumps, and rubella vaccines. In general, these parenterally administered live vaccines should not be given for at least 6 weeks, and preferably 3 months, after IG administration. However, the postpartum vaccination of susceptible women with rubella vaccine should not be delayed because of receipt of anti-Rho(D) IG (human) or any other blood product during the last trimester of pregnancy or at delivery. These women should be vaccinated immediately after delivery and, if possible, tested in 3 months to ensure that rubella immunity was established.

If administration of IG preparations becomes necessary after a live-virus vaccine has been given, interference can occur. Usually, vaccine virus replication and stimulation of immunity will occur 1-2 weeks after vaccination. Thus, if the interval between administration of live-virus vaccine and subsequent administration of an IG preparation is less than 14 days, vaccination should be repeated at least 3 months after the IG product was given, unless serologic testing indicates that antibodies were produced.

In general, there is little interaction between IG preparations and inactivated vaccines. Therefore, inactivated vaccines can be given simultaneously or at any time before or after an IG product is used. For example, postexposure prophylaxis with simultaneously administered hepatitis B, rabies, or tetanus IG and the corresponding inactivated vaccine or toxoid does not impair the immune response and provides immediate protection and long-lasting immunity. The vaccine and IG should be given at different sites, and standard doses of the corresponding vaccine should be used. Increasing the

vaccine dose volume or number of immunizations is not indicated.

HYPERSENSITIVITY TO VACCINE COMPONENTS

Vaccine components can cause allergic reactions in some recipients. These reactions can be local or systemic, including mild to severe anaphylaxis (e.g., hives, swelling of the mouth and throat, difficulty breathing, hypotension, or shock). The responsible vaccine components can derive from: 1) animal protein, 2) antibiotics, 3) preservatives, and 4) stabilizers. The most common animal protein allergen is egg protein found in vaccines prepared using embryonated chicken eggs or chicken embryo cell cultures (e.g., yellow fever, mumps, measles, and influenza vaccines). Ordinarily, persons who are able to eat eggs or egg products safely can receive these vaccines; persons with histories of anaphylactic allergy to eggs or egg proteins should not.

Asking persons whether they can eat eggs without adverse effects is a reasonable way to screen for those who might be at risk from receiving measles, mumps, yellow fever, and influenza vaccines. Protocols requiring extreme caution have been developed for testing and vaccinating with measles and mumps vaccines those persons with anaphylactic reactions to egg ingestion.² A regimen for administering influenza vaccine to children with egg hypersensitivity and severe asthma has also been developed.³

Rubella vaccine is grown in human diploid cell cultures and can safely be given to persons with histories of severe allergy to eggs or egg proteins.

Some vaccines contain trace amounts of antibiotics to which patients may be hypersensitive. The information provided in the vaccine package insert should be carefully reviewed before a decision is made whether the rare patient with such hypersensitivity should be given the vaccine(s). No currently recommended vaccine contains penicillin or its derivatives.

MMR and its individual component vaccines contain trace amounts of neomycin. Although the amount present is less than would usually be used for the skin test to determine hypersensitivity, persons who have experienced anaphylactic reactions to neomycin should not be given these vaccines. Most often, neomycin allergy is a contact dermatitis, a manifestation of a

delayed-type (cell-mediated) immune response rather than anaphylaxis. A history of delayed-type reactions to neomycin is not a contraindication for these vaccines.

Bacterial vaccines, such as cholera, DTP, plague, and typhoid, are frequently associated with local or systemic adverse effects, such as redness, soreness, and fever. These reactions are difficult to link with a specific sensitivity to vaccine components and appear to be toxic rather than hypersensitive. On rare occasions, urticarial or anaphylactic reactions in DTP, DT, or Td recipients have been reported. When such events are reported, appropriate skin tests should be performed to determine sensitivity to tetanus toxoid before its use is discontinued.⁴

ALTERED IMMUNOCOMPETENCE

Virus replication after administration of live, attenuated-virus vaccines can be enhanced in persons with immunodeficiency diseases and in persons with suppressed capacity for immune response as occurs with leukemia, lymphoma, generalized malignancy, symptomatic HIV infections, or therapy with alkylating agents, antimetabolites, radiation, or large amounts of corticosteroids. Severe complications have followed vaccination with live, attenuated-virus vaccines and with live-bacteria vaccines (e.g., BCG) in patients with leukemia, lymphoma, or suppressed immune responses. In general, these patients should not be given live vaccines, with the exceptions noted below.

If polio immunization is indicated for immunosuppressed patients, their household members, or other close contacts, these persons should be given IPV rather than OPV. Although a protective immune response cannot be assured in the immunocompromised patient, some protection may be provided. Because of the possibility of immunodeficiency in other children born to a family in which one such case has occurred, no family members should receive OPV unless the immune statuses of the intended recipient and all other children in the family are known.

Patients with leukemia in remission whose chemotherapy has been terminated for at least 3 months can be given live-virus vaccines. Short-term, low-to-moderate dose systemic corticosteroid therapy (less than 2 weeks), topical steroid therapy (e.g., nasal,

skin), long-term alternate-day treatment with low to moderate doses of short-acting systemic steroids, and intra-articular, bursal, or tendon injection with corticosteroids are not immunosuppressive in their usual doses and do not contraindicate live-virus vaccine administration.

The growing number of infants and preschoolers infected with HIV has directed special attention to the appropriate immunization of such children. The evaluation and testing for HIV infection of asymptomatic children presenting for vaccines is not necessary before decisions concerning immunization are made. The inactivated childhood vaccines (e.g., DTP or HbCV) should be given to HIV-infected children regardless of whether HIV symptoms are present. Although OPV has not been harmful when administered to asymptomatic HIV-infected children, IPV is the vaccine of choice if the child is known to be infected. The use of IPV not only eliminates any theoretical risk to the vaccinee but also prevents the possibility of vaccine virus spread to immunocompromised close contacts. Asymptomatically infected persons in need of MMR should receive it. Also, MMR should be considered for all symptomatic HIV-infected children since measles disease can be severe in symptomatic HIV-infected children. Limited studies of MMR immunization in both asymptomatic and symptomatic HIV-infected patients have not documented serious or unusual adverse events. In addition, pneumococcal vaccine is recommended for any child infected with HIV. Influenza vaccine is recommended for children with symptoms of HIV infection.

FEBRILE ILLNESS

The decision to administer or delay vaccination because of a current or recent febrile illness depends largely on the severity of symptoms and on the etiology of the disease.

Although a moderate or severe febrile illness is reason to postpone immunizations, minor illnesses such as mild upper-respiratory infections (URI) with or without low-grade fever are not contraindications for vaccination. In persons whose compliance with medical care cannot be assured, it is particularly important to take every opportunity to provide appropriate vaccinations.

Children with moderate or severe febrile illnesses can be vaccinated as

soon as the child has recovered. This precaution to wait avoids superimposing adverse effects of the vaccine on the underlying illness or mistakenly attributing a manifestation of the underlying illness to the vaccine.

Routine physical examinations or measuring temperatures are not prerequisites for vaccinating infants and children who appear to be in good health. Asking the parent or guardian if the child is ill, postponing vaccination in those with moderate or severe febrile illnesses, and immunizing those without contraindications to vaccination are appropriate procedures in childhood immunization programs.

VACCINATION DURING PREGNANCY

Because of a theoretical risk to the developing fetus, pregnant women or women likely to become pregnant within 3 months after vaccination should not be given live, attenuated-virus vaccines. With some of these vaccines—particularly rubella, measles, and mumps—pregnancy is a contraindication. Both yellow fever vaccine and OPV, however, can be given to pregnant women who are at substantial risk of exposure to natural infection. When a vaccine is to be given during pregnancy, waiting until the second or third trimester is a reasonable precaution to minimize concern over teratogenicity. Although there are theoretical risks, there is no evidence of congenital rubella syndrome in infants born to susceptible mothers who inadvertently were given rubella vaccine during pregnancy.

Persons given measles, mumps, or rubella vaccines can shed but not transmit these viruses. These vaccines can be administered safely to the children of pregnant women. Although live polio virus is shed by persons recently immunized with OPV (particularly after the first dose), this vaccine can also be administered to the children of pregnant women because experience has not revealed any risk of polio vaccine virus to the fetus.

There is no convincing evidence of risk to the fetus from immunizing the pregnant woman with inactivated virus or bacteria vaccines or toxoids. Previously immunized pregnant women who have not received a Td immunization within the last 10 years should receive a booster dose once past the first trimester. Women who are unimmunized or only partially immunized against tetanus should complete

as much of the primary series as possible during the last two trimesters of the pregnancy. Depending on when the woman seeks prenatal care and the required interval between doses, one or two doses of Td can be administered before delivery. Eligible women who do not complete the required three-dose series during pregnancy should be followed after delivery to assure they receive the doses necessary for protection.

All pregnant women should be evaluated for immunity to rubella. Women susceptible to rubella should be immunized immediately after delivery. In addition, a woman's status as a carrier of hepatitis B should also be assessed during pregnancy. A woman infected with hepatitis B virus should be followed carefully so that her child can receive HBIG and the hepatitis B vaccine series shortly after delivery. There is no known risk to the fetus from passive immunization of pregnant women with IG. Further information regarding immunization of pregnant women is available in the American College of Obstetricians and Gynecologists Technical Bulletin Number 64, May 1982.

MISCONCEPTIONS CONCERNING CONTRAINDICATIONS TO VACCINATION

Some health-care providers inappropriately consider certain conditions or circumstances contraindications to vaccination. Conditions most often inappropriately regarded as routine contraindications include the following:

1. Reaction to a previous dose of DTP vaccine that involved only soreness, redness, or swelling in the immediate vicinity of the vaccination site or temperature of less than 105 F (40.5 C).
2. Mild acute illness with low-grade fever or mild diarrheal illness in an otherwise well child.
3. Current antimicrobial therapy or the convalescent phase of illnesses.
4. Prematurity. The appropriate age for initiating immunizations in the prematurely born infant is the usual chronologic age. Vaccine doses should not be reduced for preterm infants.
5. Pregnancy of mother or other household contact.
6. Recent exposure to an infectious disease.
7. Breastfeeding. The only vaccine virus that has been isolated from breast milk is rubella vaccine virus. There is no good evidence that breast milk from

women immunized against rubella is harmful to infants.

8. A history of nonspecific allergies or relatives with allergies.

9. Allergies to penicillin or any other antibiotic, except anaphylactic reactions to neomycin (e.g., MMR-containing vaccines) or streptomycin (e.g., OPV). None of the vaccines licensed in the United States contain penicillin.

10. Allergies to duck meat or duck feathers. No vaccine available in the United States is produced in substrates containing duck antigens.

11. Family history of convulsions in persons considered for pertussis or measles vaccination.^{5,6}

12. Family history of sudden infant death syndrome in children considered for DTP vaccination.

13. Family history of an adverse event, unrelated to immunosuppression, following vaccination.

ADVERSE EVENTS FOLLOWING VACCINATION

Modern vaccines are safe and effective but not completely so. Adverse events have been reported following the administration of all vaccines. These events range from frequent, minor, local reactions to extremely rare, severe, systemic illness, such as paralysis associated with OPV. It is often impossible to establish evidence for cause-and-effect relationships when untoward events occur after vaccination because temporal association alone does not necessarily indicate causation. More complete information on adverse reactions to a specific vaccine may be found in the ACIP recommendations for each vaccine.

The National Vaccine Injury Compensation Program established by the National Childhood Vaccine Injury Act of 1986 requires physicians and other health-care providers who administer vaccines to maintain permanent immunization records and to report occurrences of certain adverse events to the U.S. Department of Health and Human Services. Recording and reporting requirements took effect on March 21, 1988. Reportable reactions include those listed in the Act for each vaccine^{7,8} and events specified in the manufacturer's vaccine package insert as contraindications to further doses of that vaccine. Although there will be one system for reporting adverse events following immunizations in the future, at present there are two separate systems. The

appropriate method depends on the source of funding used to purchase the vaccine. Events that occur after receipt of a vaccine purchased with public (federal, state, and/or local government) funds must be reported by the administering health provider to the appropriate local, county, or state health department. The state health department completes and submits the correct forms to CDC. Reportable events that follow administration of vaccines purchased with private money are reported by the health-care provider directly to the Food and Drug Administration (FDA).

PATIENT INFORMATION

Parents, the responsible caregiver, or adult patients should be informed about the benefits and risks of vaccine in understandable language. Ample opportunity for questions and answers should be provided before each immunization. CDC has developed "Important Information Statements" for use with federally purchased vaccines given in public health clinics, but similar statements have not been universally adopted for the private medical-care sector.

An Important Information Statement must be developed for each vaccine covered by the National Childhood Vaccine Injury Act (DTP or component antigens, MMR or component antigens, IPV, and OPV). These statements are to be used by all public and private providers of vaccines. Until the Important Information Statements established by the Act become available the current CDC Important Information Statements should be used in public health clinics and other settings where publicly purchased vaccines are used. The use of similar statements in the private sector is encouraged.

VACCINE PROGRAMS

The best way to reduce vaccine-preventable diseases is to have a highly immune population. Universal immunization is an important part of good health care and should be accomplished through routine and intensive programs carried out in physicians' offices and in public health clinics. Programs aimed at ensuring that all children are immunized at the recommended ages should be established and maintained in all communities. In addition, appropriate immunizations should be available for all adults.

Every visit to a health-care provider

is an opportunity to update a patient's immunization status with needed vaccines. All adults should complete a primary series of tetanus and diphtheria toxoids, then receive a booster dose every 10 years. Persons greater than or equal to 65 years old and all adults with medical conditions that place them at risk for pneumococcal disease or serious complications of influenza should receive one dose of pneumococcal polysaccharide vaccine and annual injections of influenza vaccine. In addition, immunization programs for adults should provide MMR vaccine whenever possible to anyone believed susceptible to measles, mumps, or rubella. Use of MMR ensures that the recipient has been immunized against three different diseases and causes no harm if the vaccinee is already immune to one or more of its components.

Official health agencies should take necessary steps, including developing and enforcing school immunization requirements, to assure that students at all grade levels, including college students, and those in child-care centers are protected against vaccine-preventable diseases. Agencies should also encourage institutions such as hospitals and extended-care facilities to adopt policies regarding the appropriate immunization of residents and employees.

Dates of immunization (day, month, and year) should be recorded on institutional immunization records, such as those kept in schools and child-care centers. This will facilitate assessments that a primary vaccine series has been completed according to an appropriate schedule and that needed boosters have been obtained at the correct time.

Tickler or recall systems can identify children who are due for immunizations or are behind schedule so parents can be contacted and reminded to have their children immunized. The ACIP recommends the use of these systems by all health-care providers. Such systems should also be developed by health-care providers who treat adults to ensure that at-risk persons receive influenza vaccine annually.

IMMUNIZATION RECORDS

Documentation of patient immunizations will help ensure that persons in need of vaccine receive it and that adequately vaccinated patients are not overimmunized with increased risk of hypersensitivity (e.g., tetanus toxoid hypersensitivity).

Patient's Personal Record

Official immunization cards have been adopted by every state and the District of Columbia to encourage uniformity of records and to facilitate the assessment of immunization status by schools and child-care centers. The records are also important tools in immunization education programs aimed at increasing parental and patient awareness of the need for vaccines. A permanent immunization record card should be established for each newborn infant and maintained by the parent. In many states, these cards are distributed to new mothers before discharge from the hospital.

Provider Records

The National Vaccine Injury Compensation Program requires each health-care provider to record in the vaccine recipient's permanent medical record (or in a permanent office log or file) the provider's name, address, and title (if appropriate), the type of immunobiologic administered, the manufacturer, lot number, and date of administration. Health-care provider is any licensed health-care professional, organization, or institution, whether private or public (including federal, state, and local departments and agencies), under whose authority a specified vaccine is administered. The vaccines covered under this new law include: DTP and MMR (or any of their components given singly or in combination), OPV, and IPV. A permanent immunization record should also be established and maintained for adults and children who receive vaccines not covered by the National Vaccine Injury Act. The ACIP recommends use of standard records that note the type, manufacturer, lot number, and date of administration for each immunobiologic administered. Serologic test results for vaccine-preventable diseases, such as those for rubella screening, as well as documented episodes of adverse events, should also be recorded in the vaccine recipient's permanent medical record.

SOURCES OF VACCINE INFORMATION

In addition to these general recommendations, the practitioner can draw on a variety of sources for specific data and updated information including: Official vaccine package circulars. Man-

ufacturer-provided product-specific information approved by the FDA with each vaccine. Some of these materials are reproduced in the Physician's Desk Reference (PDR).

Morbidity and Mortality Weekly Report (MMWR). Published weekly by CDC, MMWR contains regular and special ACIP recommendations on vaccine use and statements of vaccine policy as they are developed and reports of specific disease activity. Subscriptions are available through Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402. Also available through MMS Publications, C.S.P.O. Box 9120, Waltham, MA 02254.

Health Information for International Travel. Booklet published annually by CDC as a guide to national requirements and with recommendations for specific immunizations and health practices for travel to foreign countries. Purchase from the Superintendent of Documents (address above).

Advisory memoranda are published as needed by CDC to advise international travelers or persons who provide information to travelers about specific outbreaks of communicable diseases abroad. They include health information for prevention and specific recommendations for immunization. Memoranda and/or placement on mailing list are available from Division of Quarantine, Center for Prevention Services (CPS), CDC, Atlanta, GA 30333.

The Report of the Committee on Infectious Diseases of the American Academy of Pediatrics (Red Book). This report, which contains recommendations on all licensed vaccines, is updated every 2-3 years, most recently in 1988. Policy changes for individual recommendations for immunization practices are published as needed by the American Academy of Pediatrics in the journal *Pediatrics*. They are available from American Academy of Pediatrics, Publications Division, 141 Northwest Point Blvd., P.O. Box 927, Elk Grove Village, IL 60009-0927.

Control of Communicable Diseases in Man is published by the American Public Health Association every 5 years, most recently in 1985 (14th ed.) The manual contains information about infectious diseases, their occurrence worldwide, diagnoses and therapy, and up-to-date recommendations on isolation and other control meas-

ures for each disease presented. It is available from the American Public Health Association, 1015 Fifteenth St. N.W., Washington, DC 20005.

Guide for Adult Immunization (1985) is produced by the American College of Physicians for physicians caring for adults. It emphasizes use of vaccines in healthy adults and adults with specific disease problems. It is available from American College of Physicians, Division of Scientific Activities, Health and Public Policy, 4200 Pine Street, Philadelphia, PA 19104.

Technical bulletins of the American College of Obstetricians and Gynecologists are updated periodically. These bulletins contain important information on immunization of pregnant women. They are available from American College of Obstetricians and Gynecologists, Attention: Resource Center, 409 12th Street S.W., Washington, DC 20024-2188.

State and many local health departments frequently provide technical advice, printed information on vaccines and immunization schedules, posters, and other educational materials.

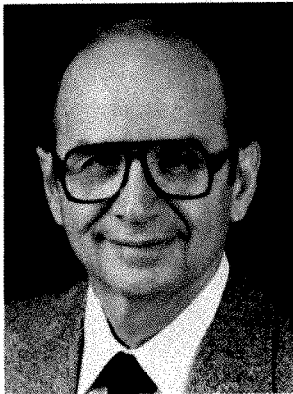
Division of Immunization, CPS, CDC, Atlanta, GA 30333, telephone (404) 639-3311, offers technical advice on vaccine recommendations, disease outbreak control, and sources of immunobiologics. In addition, a course on the epidemiology, prevention, and control of vaccine preventable diseases is offered each year in Atlanta and, on occasion, in different states.

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The Editorial Board Speaks . . .

Milton Arnold, MD



In his tenure with us, Milt has more than earned our respect and admiration. He has worked tirelessly on the many tasks assigned to him and completed them with dispatch. Our previous biographical sketch (*AJDC*. 1987;141:610) outlined his many accomplishments. Added to these is a new grandchild, of whom he and Sylvia are justifiably proud and indulgent. He has one of the most active "retirements" of anyone I've known.

His contribution below is particularly cogent for today's generation of physicians. Not "born" to the computer age, many of us have had to struggle to get there, as we watched our youngsters flip through the keys and master the technology with little discomfort or distress. Milt captures the sentiments of many as he describes a new marriage, one that he falsely claims "threatens" his longer and much happier one. Many of our readers will recognize his feelings. Enjoy!

COMPUTER TIMIDITY: SOME THOUGHTS

Can a long-existing marriage survive the presence of a computer? In sickness and in health, for better or for worse, until death do you part; nowhere in our 39-year-old Katuba (marriage contract) is there mention of a computer and it's potential for inanimate infidelity and occasional bouts of manic-depressive behavior.

The courtship between the computer and me was long and stormy. It was full of distrust, intimidation, and frustration. The generational gap was evident. My godchild, at 5 years of age, was studying English and Spanish grammar on her Apple computer. My three score plus years provided little more than confusion.

Age alone should entitle me to some seniority and wisdom, but this device created by the "Baby Boomers" was their consummate revenge. "Never trust anyone under 60."

With the computer, there developed a whole new vocabulary designed to confound: BITS, BYTES, RAM, ROM, DOS, D-BASE—certainly enough new acronyms to create a rebirth of the "New Deal." Other words that were familiar now had new definitions: mouse, floppy, default, icons, menu, wraparound, and the ever-present euphemism, "user friendly." The teachers of this new craft seemed hardly old enough to shave (cheeks or legs), and their demeanor, albeit friendly, was confrontational to this naive mind. I could procrastinate no longer since I was well overdue for my midlife change. The computer would reluctantly be accepted along with other less palatable modifications in my life-style, such as low-cholesterol meals and exercise. The MacIntosh joined our family.

For historical clarity, let it be known that my office had been computerized for more than two decades for fiduciary purposes. It was plethoric with an accumulation of reams of printed numbers, which were saved for reasons not yet clear. My relationship with that computer was both suspect and via an intermediary.

I now have a personal computer (PC), which suggests some sort of an intimate relationship, and there has been no third party to referee or mediate our disputes. This is somewhat akin to child rearing without the annoyance of Pampers. In both cases, one tries to share a common language, ask and answer questions, establish authority, and gain satisfaction in molding the resulting product. The computer assumes human qualities. At times it makes impudent comments, cajoles, and asks threatening questions that suggest Armageddon is not far off. My PC has icons that smile or pout depending on my actions.

Eventually, one succumbs to the challenge. Marital obligations are threatened as the "USER" works late into the night to gain control or find the information that has disappeared from the monitor due to some ill-chosen command. Like Walter Mitty, I changed personas and found myself in the airport tower moving words and phrases in lieu of wide-body jets. Even in my imagination, I lacked modernity. The contemporary Mitty would be Captain James T. Kirk on the *Starship Enterprise*.

There is some time spent in experiential learning until one feels confident that the computer understands the limits of its turf and our mutual pecking order. The latter is short-lived, and periodic "flash-backs" are inevitable.

The word processor permits even the most unskilled typist to swiftly correct errors, reroute whole paragraphs, or place them on hold until their presence is requested. Inept decisions are avoided by bells associated with comments like, "Are you sure you want to discard this paragraph?" It makes one pause and think about a previous action or at least question the computer's assertiveness. The machine is addictive, and with the almost limitless supply of innovative software, more and more tasks are assigned to it. Chores, such as consulting a dictionary or thesaurus, are accomplished by touching a couple of keys.

The PC has broadened my options for continuing medical education by accessing the literature rapidly and precisely. The addition of a modem provides such convenience at the time and place of one's choosing. Merely furnish the computer with any of the following to initiate a literature search: subject, author (if you have a preference), any limitations you may wish to include (age, gender, language, range of years to be reviewed), and shortly there appears on the screen abstracts of articles from which you may select. The whole process takes minutes, even for the unskilled. The PC leads you through the sequence, and no complex series of commands must be memorized.

Computer graphics enable the production of inexpensive slides and most printed materials from newsletters to personalized anniversary cards, which endears the PC to the family who wonders where your leisure hours are spent.

Remember, it is not necessary to understand a computer to use it. Computer intimidation and humiliation subside when the owner recognizes this is but a machine, invented by humans, and thus far subject to their control . . . perhaps.

Computers in Medicine

Augmenting Medical Care in Pediatric Patients With Chronic Illnesses

Eric G. Handler, MD, MPH

• The use of computers to aid care for chronically ill pediatric patients is a relatively new concept. We are currently using Filemaker II software and a Macintosh Plus computer to augment overall patient care in children with chronic diseases, such as spina bifida, cerebral palsy, neuromuscular diseases, head injury, and spinal cord injury. This is a computerized medical record with a clinical database for dissemination of information to multidisciplinary team members, generating letters to private health care providers, displaying telephone messages, and assisting inpatient care. Advances in computer technology will provide future applications to aid health care providers in caring for patients with chronic illnesses.

(AJDC. 1989;143:1021-1023)

Computers have been used for medical purposes for several years in the administrative, business, and laboratory fields. However, personal computers have had limited applications in direct patient care for outpatients as well as inpatients.¹⁻³ We are currently utilizing a personal computer for direct patient care in our pediatric rehabilitation population. The benefits are boundless, and with continued rapid technological advances, further applications will be identified.

MATERIALS AND METHODS

Equipment

Computer System.—We use an Apple Macintosh Plus personal computer (Apple Computer Inc, Cupertino, Calif) with 1 megabyte of random-access memory and a 20-megabyte hard disk.

Software.—We use Filemaker II (Claris

Corp, Mountain View, Calif), a flat file database (not a relational structure) that has multiuser capabilities. The program has multiuser and network capabilities.

Printer.—We use an Imagewriter II printer (Apple Computer Inc).

Terminology and Definitions

A *file* is a Macintosh document. A *record* is all the information about one item, person, or transaction. A file is composed of any number of records containing data. The individual components of a record are *fields*. A *layout* is an arrangement of objects that can be used to control the way information looks on the screen and on paper. Each layout is completely separate from the data; the layout controls the appearance, not the content.

Methods

The basic layout for the computerized medical record was developed in approximately 1 hour. Modifying the layouts for different clinics required less than 15 minutes. The layouts can be accessed by simple menu operations or by scripts that expedite the process by using keyboard commands.

Depending on the amount of material contained in a given layout, information can be entered rather quickly even when using a two-finger typing technique. Approximately 5 minutes is needed to update the computer information obtained during the patient's return visits. Initial and new visits require more time, and information is entered directly into the computer by the physician after clinic hours.

Hospital #		B.D.		Date of last visit		Date	
Address		PMD		Equipment		Insurance	
Phone		Consult					
PHYSICIAN EXAM		HEENT		GEN		SCHEDULE	
S.P.		CHEST		SKIN			
Head		ABD		NEURO			
Weight		BACK					
Height		EXT					
MEDICATION		IMMUNIZATION		DIET			
		ALLERGIES		SERIOUS ILLNESS-HOPE			
NEUROSURGERY		ORTHO		PT-OT-SPEECH			
BLADDER-BOWEL				SKIN			
AUDIO-VISUAL-DENTAL		SCHOOL		LAB			
PSYCHOSOCIAL							
RECOMMENDATIONS							

ERIC G. HANDLER M.D., M.P.H.
DIRECTOR OF SPINA BIFIDA

Fig 1.—Spina bifida clinic layout.

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Reprint requests to The Nisonger Center, 1561 Dodd Dr, Columbus, OH 43210-1205 (Dr Handler).

Hospital		B.D.	Date of last visit	Consult	Date
Address	PMD	REFERRING MD	Equipment	Insurance	
Phone					
PHYSICAL EXAM	HEENT	EXT			
B.P.	CHEST	NEURO			
Head	HEENT				
Weight	ABD				
Height	BACK				
	GEN				
	SKIN				
MEDICATION	VACCINATIONS	DIET			
	ALLERGIES	SERIOUS ILLNESS/HOSP			
NEUROLOGY		ORTHO	PT-OT-SPEECH		
BLADDER-BOWEL		HOSP-SURG	SKIN		
PULMONARY		PSYCHOSOCIAL	LAB		
SCHOOL	AUDIO-VISUAL-DENTAL				
PROBLEM LIST	RECOMMENDATIONS				
ERIC G. HANDLER M.D., M.P.H. DIRECTOR OF PEDIATRIC REHABILITATION					

Fig 2.—Spinal cord injury layout.

COMMENT

We currently have information on approximately 250 pediatric rehabilitation patients entered in the flat file database Filemaker II. There are several patient diagnostic categories: spina bifida, cerebral palsy, head injury, neuromuscular diseases, and spinal cord injury. These children have a multitude of complex problems requiring a multidisciplinary team approach to help in their management. Our team consists of a pediatrician, pediatric rehabilitation psychologist, nurse, physical and occupational therapists, medical social worker, and several subspecialists, such as a neurosurgeon, orthopedist, and urologist.

The type of program layout implemented depends on the patient's diagnosis. For example, Fig 1 demonstrates the layout for the spina bifida clinic. Each patient's record includes several sections consisting of different fields: general patient information, problem-oriented records containing current

medical evaluations and examinations, physical examination, and clinic recommendations. Each field contains previous laboratory test results as well as individual evaluations by the different team members.

A layout for patients with spinal cord injury contains slightly different informational fields (Fig 2). These patients can have significant pulmonary problems, so an additional field is added. However, the basic informational core remains unchanged.

A clinic review process occurs prior to the patient's visit, and team members are given copies of the patient's last computer-generated clinical record. This has several observed benefits: (1) Medical students, interns, and residents rotate through the clinic weekly. A standardized form allows for consistency in obtaining pertinent information during the patient's visit and provides a sense of continuity in overall patient care. (2) The families are not repeatedly asked the same questions by

different team members during a clinic visit. (3) Chart reviews are not necessary before the patient's visit. This allows more time to address the patient's present problems and concerns. (4) One does not have to rely on the hospital chart being available during the clinic visit. (5) Duplication of tests and ordering unnecessary laboratory work are less likely when all the previous laboratory test results are immediately available to all team members.

The patient information is manually updated on the worksheet and then directly entered into the computer. The record is printed on hospital stationery and placed directly into the chart within 2 days. A simple cover letter is sent to the private physician with a copy of the computerized clinical record. There is no longer a need to dictate notes on the patient's clinic visit. The clinic record is a single page, is easy to read, and contains only pertinent clinical information (Fig 3). Private practitioners have been grateful for being able to review this information quickly instead of having to read the normal lengthy dictations. The computer database can also generate a cover letter to the care provider that can include specific information directed to a physician specialty, such as orthopedics or neurosurgery. This is accomplished by linking fields in the letter layout with specific informational fields in another layout.

Another example of informational linking among layouts is the telephone message display (Fig 4). When a parent or patient calls the clinic, one can enter the patient's name into the name field, which results in immediate retrieval of selected patient information from the most recent clinic visit. The conversation is directly entered into the database and can become a permanent part of the patient's medical record. One does not have to wait until the medical records arrive before calling the family. This allows for quick return of calls, aids consistency in treatment, and decreases the potential for misunderstandings.

There are additional advantages to a computerized medical record. Every word entered into the individual fields is indexed so that this information can be readily retrieved for research, and further data manipulations can be performed by easily exporting the informa-

PATIENT'S NAME		Hospital #	S.D.	Date of last visit	7/25/88	Date	4/4/89
Address DANE COUNTY		PMD HANDLER	Equipment WC	SWIVAL WALKER	Insurance	MEDICAL ASSISTANCE	
Phone (608) 555-1212				Consult		8/9/88	
S.P. 90/70		HEENT		BILATERAL EAR TUBES		GEN	
		CHEST		CLEAR WITHOUT RALES		DISPLACED URETERAL MEATUS	
		HEART		NORMAL SINUS RHYTHM		SKIN	
		ABD		VISCEROTOMY		NO PRESSURE SORES OR RASHES	
Weight 15KG		BACK		4X4CM BULGE LOWER LUMBAR		NEURO	
Height 78.5CM		EXT		BILATERAL KNEE AMPUTATIONS		CRANIAL NERVES INTACT	
		UPPER EXTREMITIES		NORMAL STRENGTH		DTR NORMAL UPPER EXTREMITY	
						L2 MOTOR LEVEL	
HYPERKALEMIA, BIL AMPUT.		IMMUNIZATIONS		DTP		1/88 BILATERAL LEG	
SEPTRA 1 TEASPOON DAILY		ALLERGIES		NONE		AMPUTATION	
INDEROL 15MG-10MG-15MG						8/88 EVALUATION FOR	
NAHCO3 SCC FOUR TIMES DAILY						UROLOGICAL SURGERY	
NEUROSURGERY		CALCULUS		REGRESSIVE SYNDROME		PT-OT-SPEECH	
MENINGITIS 4/84		T12		LOWEST NORMAL VERTEBRAL BODY		TRUNK BALANCE GOOD. SCOOTERS ON	
NO HYDROCEPHALUS		1/88		BILATERAL KNEE AMPUTATION		BUTT. ABLE TO STAND ON HEAD	
NO SHUNT						PHYSICAL AND OCCUPATIONAL	
						THERAPY 1 TIME PER WEEK	
						SOCALLY VERY INDEPENDENT	
BLADDER-BOWEL		TYPE 4		RENAL TUBULAR ACIDOSIS		VERMICOTOMY 8/85	
						NO UTI SINCE 8/85	
						1985 RENAL SCAN RIGHT 86% LEFT 7%	
						LEFT ECTOPIC KIDNEY, RT URETER DILATED.	
						298 IVE: CROSSED FUSED ECTOPIA ON THE RIGHT. 347 RENAL US	
						BILATERAL HYDRONEPHROSIS	
						AND HYDROURETER. 888 UROLOGY APPOINTMENT: URETERAL DILATION, IVE: FUNCTION ON ON	
						RIGHT KIDNEY AND HYDRONEPHROSIS. RENAL BLADDER US NO CHANGE	
						11/88 HAD CYSTOSCOPY TO EVALUATE FOR POTENTIAL SURGERY. RT 3/88	
CONDOMS 2XSP DAILY FOR BOWEL MANAGEMENT						SKIN	
AUDIO-VISUAL-RENTAL						NO PRESSURE SORES OR RASHES	
1/88 DENTAL							
AUDIO 1987							
NEVER HAD VISION TESTED		SCHOOL		EARLY CHILDHOOD PROGRAM WILL BE		LAB	
				STARTING FIRST GRADE.		URINE CULTURE	
						ELECTROLYTES	
PSYCHOSOCIAL		DOING WELL SOCIALLY. MANY FRIENDS.					
		TESTED 2 GRADES HIGHER IN SCHOOL.					
		MOM WITH DIABETES. SISTER BORN 1977 AND BROTHER BORN					
		1988					
		1980 MOM WORKS AS A LAB TECHNICIAN					
		1980 DAD WORKS AT A FACTORY					
RECOMMENDATIONS		RETURN IN 3 MONTHS TO SEE ORTHOPEDICS AND UROLOGY.		ERIC G. HANDLER M.D., M.P.H.		PATIENT'S NAME	
		OBTAIN THERAPY RECORDS.		DIRECTOR OF SPINA BIFIDA			
		WILL DISCUSS WITH UROLOGY FUTURE SURGICAL PLANS AND					
		COORDINATE ADMISSION					
		DISCUSS WITH PATIENT SURGICAL ADMISSION					
		ORTHOTICS TO MODIFY SWIVAL WALKER AND WHEELCHAIR					

Fig 3.—Spina bifida clinical record.

DATE OF CALL 4/5/89		TIME 9 AM	
NAME PATIENT'S NAME		PHONE NUMBER (608) 555-1212	
ADDRESS DANE COUNTY		PMD HANDLER	
CLINIC VISIT 4/4/89		LAST CLINIC VISIT 7/25/88	
ALLERGIES NONE		MEDS SEPTRA 1 TEASPOON DAILY	
		INDEROL 15MG-10MG-15MG	
		NAHCO3 SCC FOUR TIMES DAILY	
MESSAGE ASKING FOR CLARIFICATION OF THE SURGICAL PROCEDURE		REC RETURN IN 3 MONTHS TO SEE ORTHOPEDICS AND UROLOGY.	
WHAT TIME TO CHECK PATIENT INTO THE HOSPITAL		OBTAIN THERAPY RECORDS.	
		WILL DISCUSS WITH UROLOGY FUTURE SURGICAL PLANS AND	
		COORDINATE ADMISSION	
		DISCUSS WITH PATIENT SURGICAL ADMISSION	
		ORTHOTICS TO MODIFY SWIVAL WALKER AND WHEELCHAIR	
DURATION OF CALL 10 MINUTES			

Fig 4.—Telephone messages.

tion to statistical analysis computer programs. For example, we wanted to determine the number of spina bifida patients with diagnosed tethered cord. We evaluated the orthopedic, neurosurgical, and urologic consequences of untethering spinal cords as opposed to not performing this surgical procedure. The computer program allowed immediate access to this material. To obtain this

information by conventional means would have been extremely cumbersome and time-consuming.

Information that is of a sensitive or confidential nature can be hidden in the printout. The field box has a predefined number of lines, and words that extend beyond these boundaries appear only when the field is activated. When the clinic record is printed this material is

not shown, so clinic personnel do not have access to this information. This eliminates the need for keeping separate records for confidential materials, and when medical records are requested by different people or agencies, confidentiality is maintained.

The computer program is also applied to the pediatric rehabilitation inservice. Weekly updated printouts of hospital progress notes provide a summary of care. This is extremely helpful for several reasons: (1) Medical students, interns, and residents rotate on the inpatient service on a monthly basis. Pediatric rehabilitation inpatients can be admitted for as long as 6 months to a year, so review of chart information by the new team members would be a time-consuming task. (2) On-call teams have access to up-to-date information on the different rehabilitation patients. This provides a standardized level of knowledge for each patient. (3) Updated material on inpatient care requested by agencies and insurance companies can be retrieved. (4) Discharge summaries are no longer a lengthy organizational exercise.

Computer applications for inpatient and outpatient pediatric care augment overall pediatric rehabilitation patient care and allow medical personnel to spend more interactive time with the patients and their families. It is difficult to objectively assess the clinical impact of the computerized medical record on patient care, because the pediatric rehabilitation inpatient and outpatient service was in program development at the same time. However, unsolicited feedback from various health care providers (physicians, nurses, and therapists) has been highly favorable and has included numerous requests for instructional guidance on implementing similar programs in their areas of clinical practice. Computer technology is expanding rapidly, and this will undoubtedly have a direct impact on the practice of medicine in the future.

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Cast Bronchitis in Infants and Children

Agustin Pérez-Soler, MD

• Seventy-two children (age range, 3 months to 5.5 years) with a clinical diagnosis of obstructive bronchitis (asthmoid or spastic bronchitis or bronchiolitis) were found to have bronchial casts in the gastric fluid, and in 2 additional cases casts were spontaneously expectorated in the bronchial exudate. Cast bronchitis had a long-term course of 10 to 24 months in 65 of the 74 patients. Common radiologic findings included bronchi presumably filled with secretions, areas of atelectasis, and lung emphysema of varying degrees. Cast bronchitis did not appear to be associated with eosinophilia and elevated serum IgE levels. Therefore, an extrinsic allergic mechanism is not likely involved in the pathogenesis of the condition. Bronchial casts had varying consistencies; although they were usually soft, they were sometimes rather hard. They were hollow, often ramified, and white and measured from 0.5 to 2 cm in length. Histologically, they consisted of metaplastic squamous epithelium with a varying degree of inflammatory cells and noncellular material. Some differences in biochemical composition were observed between bronchial casts and bronchial exudate of acute catarrhal bronchitis. No viruses could be isolated in 11 cast specimens. Our results suggest that cast formation is mainly related to the metaplastic transformation of the bronchial epithelium and that this metaplasia may play an important pathophysiologic role in certain infants and children with obstructive bronchitis.

(AJDC. 1989;143:1024-1029)

A form of bronchitis characterized by the production of an "organized" exudate that has the internal anatomic configuration of the respiratory tree has been repeatedly reported in adults. The expectoration of structures thought to be of a fibrinous or mucoidlike material

that are true bronchial casts rather than plugs of mucus (mucoid impaction) constitutes the differential sign of the disease.

There have been only a few reports of similar cases in children,¹⁻³ most likely because children swallow the respiratory secretions, and therefore the presence of bronchial casts can only consistently be proved by examination of the gastric fluid.

After observing two children (the first in 1942) with pronounced asthmatic symptoms who spontaneously expectorated evident tracheobronchial casts and had subsequent relief of symptoms, I hypothesized that cast formation might be a common phenomenon in infants and children with wheezing bronchitis (asthmoid or spastic bronchitis or bronchiolitis). During a long period of academic and private pediatric practice I obtained (with each family's consent) gastric fluid from 72 children who had repeated episodes of bronchitis, lasting at least 2 weeks but sometimes several months without clear remissions. Structures compatible with bronchial casts were found in all cases. The bronchial casts observed had varying consistencies; they were usually soft, although sometimes rather hard. They were hollow, often ramified, and white. My observations suggest that infants and children can be affected by an inflammatory process of the respiratory tract that results in expectoration of bronchial casts similar to the fibrinous bronchitis described years ago in adults.

A mild and chronic form of cast bronchitis is considered exceptionally rare, probably because the expectoration of bronchial exudates in children younger than 5 years of age is rare, and when it occurs the bronchial specimen is not routinely examined.

I report here on the clinical and radiologic characteristics of patients with

cast bronchitis and the microstructure and biochemical composition of the bronchial casts.

PATIENTS AND METHODS

Patients

Seventy-two children (age range, 3 months to 5.5 years) were found to have structures compatible with bronchial casts in the gastric fluid. Bronchial casts were also observed in two other children who spontaneously expectorated the bronchial secretions. All patients had symptoms of wheezing bronchitis for at least 2 weeks when they were studied. All patients were evaluated by clinical and radiologic methods. The presence of virus and the biochemical composition were investigated in bronchial casts obtained from 11 and 6 different patients, respectively. Three children older than 5 years of age with acute catarrhal bronchitis and spontaneous expectoration were used as controls in the biochemical composition studies.

Most patients included in this study were referred to me without a definite diagnosis after having been intensively evaluated at public and private hospitals and after failing to respond to conventional bronchodilator therapy.

Clinical and Laboratory Evaluation

A complete history was obtained and a physical examination was performed on all patients. All patients were followed up by me for at least 6 years after recovery. The routine radiologic and laboratory evaluation consisted of the following: posteroanterior and lateral chest roentgenograms, erythrocyte sedimentation rate, red and white blood cell counts, differential leukocyte count, and electrophoresis of serum proteins. The sweat test was performed in all 23 infants under 1 year of age and in 12 children older than 1 year who had suspicious chest roentgenogram findings. Immunoelectrophoresis and determination of serum IgE by the Prist method were performed in 8 patients. Salivary IgA levels were determined in 6 patients by immunonephelometry in the Department of Biochemistry, Ciudad Sanitaria de Barcelona, Spain. Normal serum IgE and salivary IgA values have been reported elsewhere.^{4,5}

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Bronchial Cast Studies

Gastric Fluid Collection and Examination of Casts.—The gastric fluid was obtained by oral gastric suction (lavage with normal saline solution or hygienized water) early in the morning, within 15 minutes after the patient awakened. Gastric lavage was performed early in the morning to avoid obtaining bronchial secretions that had been exposed for a long time to gastric fluid digestion. On awakening, children cough and swallow the bronchial secretions accumulated during the night. If children do not cough for 45 minutes before awakening (time of transit through the stomach of small amounts of food), it is reasonable to assume that most bronchial secretions obtained by gastric lavage will have been in the stomach for the time elapsed between awakening and the performance of the gastric lavage. Only two children (4 and 5.5 years of age) spontaneously coughed up the bronchial secretions.

The gastric suction was performed using a Rüscher catheter No. 24 for infants and No. 28 for children (Willy Rüscher AG, Walblingen, West Germany). If a thinner catheter is used, the largest casts cannot be collected.

The gastric fluid obtained was routinely placed in a Petri dish to disperse the specimen. Under these conditions the morphologic characteristics of bronchial casts are easily displayed.

I was unable to study the effect of gastric fluid from normal control children on the bronchial secretions of children with acute catarrhal bronchitis because consent by parents was not granted. Neither could consent be obtained for the performance of bronchoscopies in patients with cast bronchitis.

Microscopic Studies.—All casts were studied cytologically and in 65 of 74 cases histologically.

Cytologic Studies.—Smears of bronchial exudate were stained using the methods of May, Grunwald, Giemsa, and Papanicolaou and observed under light microscopy.

Histologic Studies.—Bronchial casts were fixed in 10% formaldehyde and alcohol, embedded in paraffin, and stained with hematoxylin-eosin. Stains for fibrin and mucin were not performed because they are not specific.

Electron Microscopic Studies.—Electron microscopic studies were performed in three cases.

Biochemical Analysis.—The biochemical composition of bronchial casts from six patients was studied by simple radial immunodiffusion and electroimmunodiffusion techniques in the Department of Biochemistry, Ciudad Sanitaria de Barcelona. Results were compared with those obtained in three cases of acute catarrhal bronchitis in children whose bronchial secretions were spontane-

ously expectorated.

Isolation of Viruses.—Isolation of viruses by culture was attempted in cast specimens obtained from 11 patients in the Department of Microbiology, Faculty of Medicine, University of Barcelona.

RESULTS

Clinical Findings

The age at onset of disease ranged from 3 months to 5.5 years (90.4% of patients were between 6 months and 3 years of age). The initial clinical picture consisted of an acute episode of obstructive bronchitis in all cases; dyspnea of variable intensity and a mild to high temperature elevation of short duration were the main symptoms. Diffuse wheezing with some or abundant rales was heard in all patients. Signs of laryngeal involvement were mild or absent.

The time from the onset of symptoms to complete resolution was less than 3 months in the acute form of the disease (3 cases), between 3 and 9 months in the subacute form (6 cases), and more than 9 months in the chronic form (65 cases). No clear relationship between age and duration of disease was found.

No clinical signs of other conditions, such as pancreatic cystic fibrosis, previous foreign-body aspiration, esophageal reflux with esophagitis, or immunodeficiency, were observed. Only two cases were associated with other diseases, one with pancreatic cystic fibrosis and one with extrinsic asthma.

In patients with chronic cast bronchitis the course of the disease was characterized by variations in the intensity of the clinical symptoms over a period of 10 to 24 months; one child and one infant could not be considered cured until 33 months and 40 months after the onset of the condition, respectively. Wheezing was usually moderate, sometimes minimal, and, after the acute phase, a persisting cough that usually occurred in the morning, on awakening, was sometimes the only manifestation of the condition. No recurrences were observed beyond 2 months after the resolution of all symptoms. Dyspnea was initially more severe in patients with acute cast bronchitis than in patients with subacute or chronic cast bronchitis but tended to decrease dramatically early in the course of the disease, probably after the elimination of the first tracheobronchial casts.

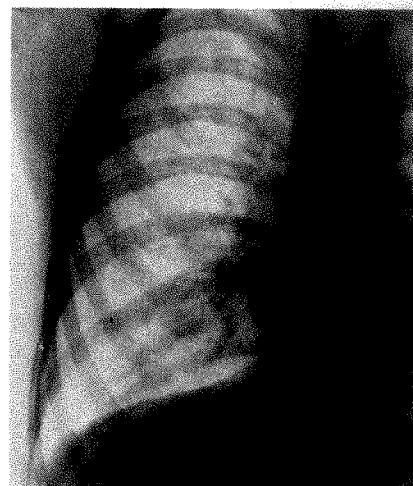


Fig 1.—Basal bronchus occupied by bronchial cast, with some more aerated portions.

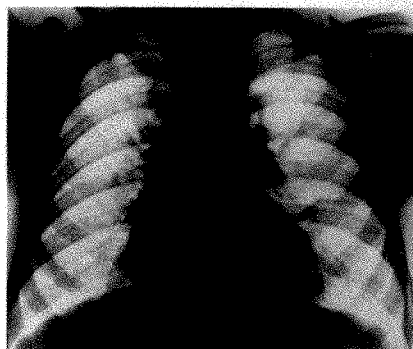


Fig 2.—Moderate lung hyperaeration and segmental atelectasis of the right lower lobe.

Radiologic Findings

Bronchi.—Partial occupation of the air space was sometimes clearly observed (Fig 1). Occupation of bronchi by secretions gave a clear cylindrical image rather than the lobulated or "botrioid" appearance associated with mucoid impaction in adults^{6,7} and with asthma⁸ and cystic fibrosis⁹ in children.

Lung Parenchyma.—Single or multiple areas of segmental, sometimes lobal, atelectasis were frequently observed (Figs 2 and 3). They usually lasted a few days, although occasionally they persisted for several weeks. Complete lung atelectasis¹ was not observed. Minimal areas of parenchymal consolidation corresponding to either small areas of atelectasis or peribronchial or perialveolar inflammation were also a common finding. Emphysematous changes of varying degree were

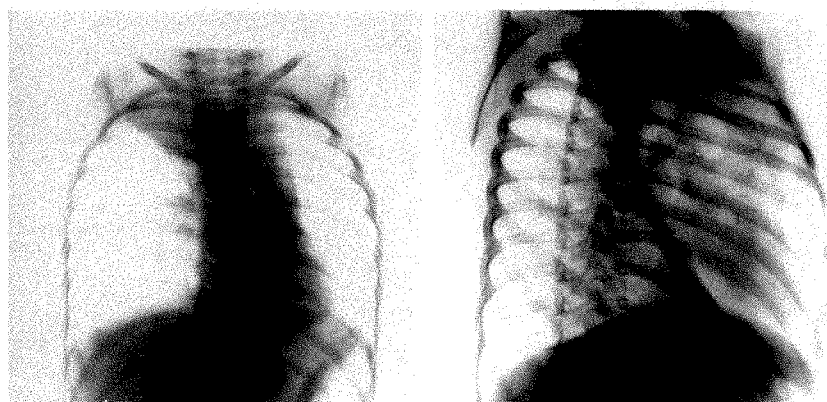


Fig 3. — Marked lung emphysema with shift of the mediastinum and two segmental atelectases, one in the right upper lobe (left) and the other in the left lower lobe (right).

Table 1. — Serum IgE Level, Blood Eosinophils, and Salivary IgA in Eight Patients With Cast Bronchitis

Patient No.	Age	Serum IgE, IU/mL	Blood Eosinophils, %	Salivary IgA, g/L
1	6 mo	33	2	...
2	2 y	18	12	...
3	3 y	6	4	0.173
4	2 y, 3 mo	250	4	0.050
5	3 y, 9 mo	161	4	0.085
6	5 y	14	2	0.090
7	5 y, 6 mo	5	3	0.010
8	2 y, 8 mo	20	6	0.050

observed in all cases, sometimes predominantly involving one hemithorax, with displacement of the heart and the mediastinum to the opposite side (Fig 3).

Laboratory Findings

The erythrocyte sedimentation rate and red and white blood cell counts were within normal limits in most cases. The leukocyte differential count consistently showed a mild lymphocytosis. In only 1 of 74 cases was there a marked eosinophilia, 35% in 1 case and 56% in the other. Neither of these 2 patients had a history of allergy, and allergic symptoms did not subsequently develop in either.

The serum protein profile was within normal limits in all patients in whom it was determined. No decrease in α_1 -globulin was observed. Serum IgE levels were normal in five of eight patients, moderately elevated in one, and mark-

edly elevated in two (Table 1). Salivary IgA levels were normal in three of six patients, slightly elevated in one, markedly elevated in one, and decreased in one (Table 1).

The sweat test was positive in only 1 of 23 children less than 1 year old and was negative in all 12 children more than 1 year old.

Bronchial Cast Studies

Physical Characteristics.—Casts obtained from patients with subacute and chronic cast bronchitis ranged from 0.5 to 2 cm in length and from 0.2 to 0.7 cm in diameter. They were normally cylindrical and often ramified. The largest casts were clearly hollow; the smallest had no apparent lumen because it was occluded by seromucous secretion, as shown by microscopic observation. Casts had varying consistencies; they were usually soft, sometimes rather hard, but never "fluid" like the muco-

purulent exudate of acute catarrhal bronchitis. They were white, sometimes light yellowish (Figs 4 and 5).

Apart from the cylindrical ramified casts, fragments of casts mixed with mucous and purulent material were also regularly observed. No Curchmann's spirals were seen in any case (macroscopically or microscopically).

Microscopic Structure.—The cytologic studies of bronchial cast smears showed the presence of an important epithelial component with a varying number of inflammatory cells (predominantly mononuclear cells in the chronic form) and noncellular fibrillar material in all cases. The epithelial component was not composed of cylindrical, ciliated-mucous epithelium as expected in the respiratory tract, but of squamous epithelium, sometimes with signs of keratinization.

The histologic study of sections of casts showed squamous metaplasia in all specimens (Figs 6 through 9). The metaplastic epithelium was the predominant cellular component in many cases. Casts composed preferentially or exclusively of metaplastic epithelium were stronger than casts with a relatively important inflammatory component (leukocytes, proteins).

Ultrastructural Changes.—No specific lesions could be assessed. The organelles, especially the mitochondria, appeared to be significantly damaged or destroyed. Organelle destruction may be due to peptic digestion by the gastric fluid or may be a manifestation of cellular degeneration, since the cells are not part of a vascularized tissue but of an exudate that is bound to necrosis.

Biochemical Composition.—Six specimens of bronchial casts were studied by radial immunodiffusion and electroimmunodiffusion. Results are shown in Table 2. Also shown in Table 2 are the results of an analysis of the biomedical composition of the bronchial secretion obtained from a representative patient with acute catarrhal bronchitis and spontaneous expectoration. Bronchial casts contained high-molecular-weight proteins, such as α_2 -macroglobulin and fibrin, that are quite viscous or that coagulate easily, while these proteins were not present or were present in smaller amounts in the bronchial exudate of patients with acute catarrhal

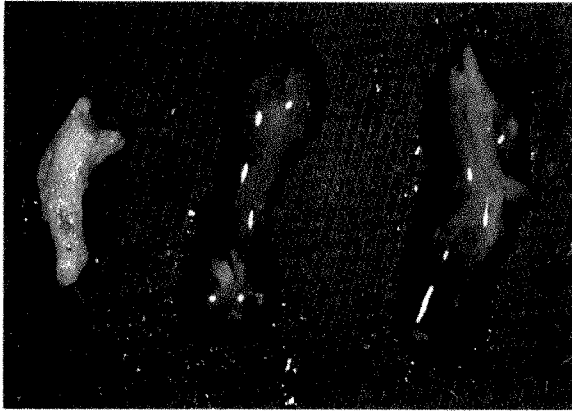


Fig 4.—Three bronchial casts. One is small and hard; the other two are softer, and one has several ramifications (original magnification $\times 2$).



Fig 5.—Bronchial casts in liquid medium. The larger one is concave.

Fig 6.—Bronchial cast. Low-power magnification of a histologic study. Several groups of squamous metaplastic cells can be seen within groups of lymphocytes (hematoxylin-eosin, original magnification $\times 100$).

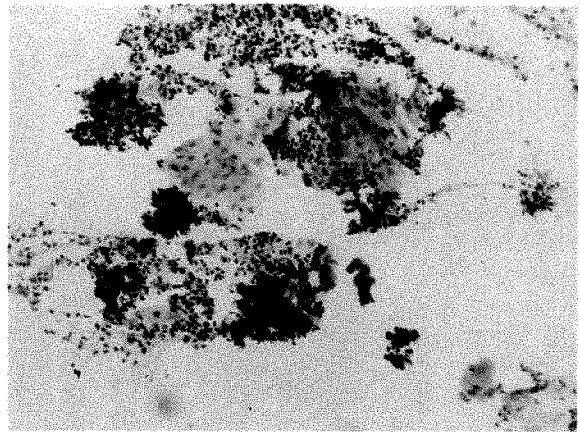
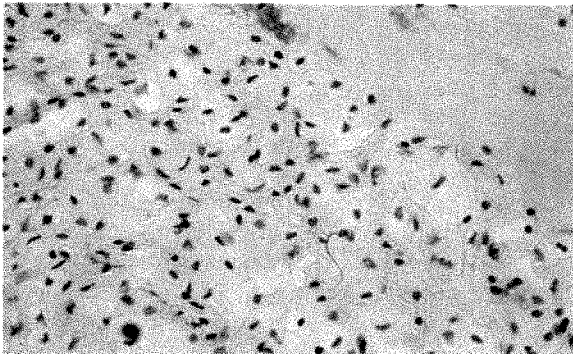


Fig 7.—This is a middle-power magnification of cells from the same patient as in Fig 6. A group of squamous metaplastic cells is visible in the center with some leukocytes. Note the vacuolated appearance of the cells. This is a usual finding in squamous metaplastic cells (hematoxylin-eosin, original magnification $\times 400$).

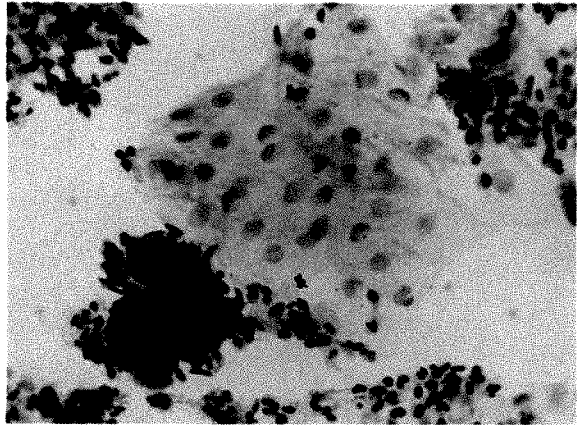


Fig 8.—This is a high-power magnification of the cells in Fig 7. Note the appearance of the basal cells, some of which show vacuolation. A keratinized cell can be seen amid polymorphonuclear leukocytes (hematoxylin-eosin, original magnification $\times 800$).

Fig 9.—Histologic section. This is a fragment of a large bronchial cast. It consists of a great clump of polygonal clear cells, more or less vacuolated. On one side, coagulated fibrillar material is seen (hematoxylin-eosin, original magnification $\times 400$).

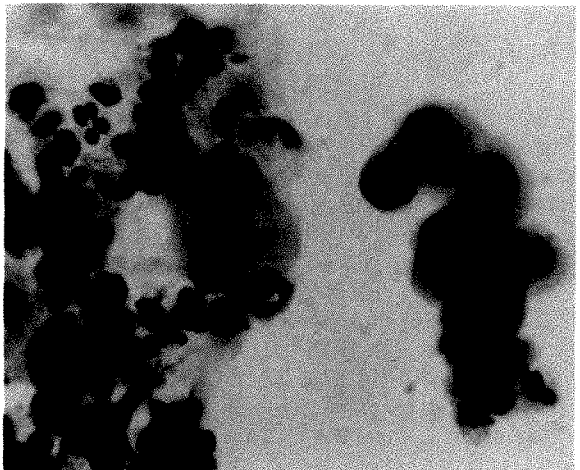


Table 2.—Biochemical Composition of Bronchial Casts

Component	% of Total Weight						Acute Catharral Bronchitis
	Cast Bronchitis by Patient No.						
	1	2	3	4	5	6	
Albumin	54.03	50.69	47.59	40.58	41.18	62.46	51.11
α_1 -Glycoprotein	3.24	3.64	3.85	3.51	...	2.64	3.96
α_1 -Antitrypsin	0.64	0.54	0.61	1.08	1.38	0.32	0.85
β -Glycoprotein	1.01	1.34	1.40	1.24	1.38	1.32	1.30
Gamma globulin	0.64	0.50	0.90	0.86	0.96	1.24	0.71
Ceruloplasmin	0.06	0.20	0.24	0.27	0.40	0.19	0.19
α_2 -Glycoprotein	1.29	1.86	1.49	1.67	2.40	1.28	1.64
Haptoglobin	7.04	7.97	7.29	9.46	10.08	8.42	10.37
α_2 -Macroglobulin	3.24	3.18	3.89	4.38	4.00	3.10	0.18
β_1 -Glycoprotein	0.02	0.04	0.06	0.02	0.05	0.05	0.03
Fibrin	4.32	5.71	5.05	5.41	6.95	5.72	0.31
β_2 -Glycoprotein	0.86	1.36	1.60	1.08	1.60	1.17	5.72
IgG	13.39	12.53	16.31	18.93	17.96	7.49	14.05
IgA	10.15	10.36	9.63	11.48	11.47	7.67	9.79

ronchitis. On the other hand, the content of β_2 -glycoprotein in the bronchial exudate of patients with acute catarrhal bronchitis was more than threefold higher than in the casts.

Virus Isolation.—Results of all virus isolation studies were negative.

COMMENT

My study strongly suggests that a significant number of children classified as chesty child¹⁰ may be affected by an acute or chronic type of bronchitis characterized by the formation of bronchial casts. The diagnosis of cast bronchitis is made by examination of the bronchial secretions in the gastric fluid, since children less than 5 years old swallow the bronchial secretions, except in cases of bronchiectasis, pulmonary abscess, or whooping cough.

Eighteen of our patients had undergone extensive study for allergies and had a diagnosis of intrinsic asthma. Most of our patients with the chronic type of cast bronchitis are probably very similar, if not identical, to the 2.6% of cases reported by Labbe et al¹¹ of children with bronchiolitis who had chronic cough and functional signs of bronchial obstruction for an average period of observation of 18 months.

Many previous studies on obstructive

bronchitis (asthmatoïd or spastic bronchitis or bronchiolitis) have analyzed the clinical signs, radiologic findings, and hematologic and other laboratory measurements. A very recent study of 74 cases by Labbe et al¹¹ also included results of virologic studies in nasopharyngeal secretions and stools. Bronchial secretions were not studied.

Bronchial casts were composed mainly of metaplastic squamous epithelial cells. It is well known that physiologic desquamation of the upper gastrointestinal tract may result in the observation of isolated squamous epithelial cells in the gastric fluid.¹² In our series, however, the squamous epithelial cells were found to form cast structures, in many instances with evident ramifications. It is extremely unlikely that these structures originate on the surface of the planar pharyngeal or esophageal epithelium, since these surfaces are devoid of macroscopic anatomic invaginations.

The pathogenesis of cast bronchitis is unknown. Our initial hypothesis was that cast bronchitis might be secondary to a fibrinous type of inflammation as in diphtheria or pneumococcal infections (fibrinous cast bronchitis). The absence of a significantly greater amount of fibrin in the cast (fibrin content ranged between 4.32% and 6.99% [Table 2]) rel-

ative to blood plasma does not favor this hypothesis. The lower amount of β_2 -glycoprotein, less than 30% of that contained in the fluid exudate of acute catarrhal bronchitis, does not support the possibility that the mucous content may be a crucial factor in cast formation. On the other hand, histologic studies showing a direct relationship between the number of metaplastic cells and the strength of the casts very much favor the possibility that cast formation is mainly related to the cohesive forces that assemble the epithelial cells. The backbone of cast would be composed of clumps of epithelial cells with bridges among them and additionally held together by certain high-molecular-weight or coagulated proteins. The cast structure would be covered and would contain seromucous secretions.

Metaplastic transformation of the tracheobronchial epithelium is a well-described finding in adults, mainly secondary to chronic irritative stimulants such as tobacco smoke. Patients with asthma also have epithelial desquamation; however, their type of desquamation is completely different from that observed in patients with cast bronchitis. Sanerkin and Evans¹³ reported that the so-called creola bodies present in the bronchial exudate of patients with asth-

ma are mainly composed of epithelial cells of the typical bronchial epithelium (ciliated and mucinous cells) but not squamous epithelial cells, as found in the casts of the patients in our series.

There is little previous information on squamous metaplasia in the bronchial epithelium in childhood. In 1919, Askanazy¹⁴ reported squamous metaplasia in the tracheal and bronchial epithelium associated with viral infections ("metaplasierenden Katarrh") caused by influenza virus and some viral pneumonitis, such as measles pneumonia. The pathogenesis of squamous metaplasia remains to be determined. Nasiell¹⁵ suggested that it might be the result of a complex sequence of events starting with the disappearance of the cilia or with simple hyperactivity of the basal layer.

The etiology of cast bronchitis remains speculative. The clinical picture suggests the possibility of an allergic condition. However, in only one patient of our series could a type I hypersensitivity be proved. This patient had chronic cast bronchitis for 2 years. Subsequently, the skin tests for several al-

lergens were positive. At this writing the patient was 26 years old and had a history of chronic allergic asthma. The combination of increased serum IgE and eosinophilia in children with asthmatic bronchitis suggests extrinsic asthma.⁴ Elevation of both measurements was not found in the eight patients in whom determinations were made. Therefore, the absence of this finding in our patients with cast bronchitis suggests that an extrinsic allergic mechanism is not likely in the pathogenesis of the entity. The follow-up of at least 6 years in all cases confirms this impression. A relationship between cast bronchitis and cystic fibrosis is a second possibility. However, only one patient in our series had a positive sweat test and later developed the classic picture of cystic fibrosis.

The presence of fever, lymphocytosis, the age at onset (from 3 months to 5.5 years), the consistently negative routine bacteriologic analysis, the clinical course, and the lack of response to broad-spectrum antibiotics firmly support a viral cause. However, no viruses could be found in 11 bronchial

specimens.

Apart from wheezing, which was a common symptom in all of our patients, the population of patients described in this study is quite heterogeneous (intensity of symptoms, duration, etc). This heterogeneity suggests that squamous metaplasia of the bronchial epithelium may be a common and nonspecific finding in children with obstructive bronchitis. It may even occur in cases of obstructive bronchitis of less than 2 weeks' duration, which is very common in daily pediatric practice. Routine, careful examination of the gastric fluid is the only way to define the population of patients in whom these pathologic changes occur.

Although mainly descriptive, the findings in this report may constitute a basis for studies directed at better defining the pathophysiologic characteristics and etiology of obstructive bronchitis in infants and children.

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In Other AMA Journals

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The Medical Outcomes Study

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Purpuric Rashes in Cystic Fibrosis

Daniel V. Schidlow, MD; Howard B. Panitch, MD; Nayere Zaeri, MD; Joseph Zenel, MD; Brad E. Alpert, MD

• Sixteen patients with cystic fibrosis experienced vasculitic rashes of the lower extremities that resembled hypergammaglobulinemic purpura. The rashes were associated with increased serum gammaglobulin G levels and rather severe lung disease. The rashes are probably the expression of chronic lung infection and high antigenic load in these patients. Their appearance was associated, in most cases, with poor long-term survival. (AJDC. 1989;143:1030-1032)

The appearance of vasculitic rashes, either alone or associated with non-specific arthritis, has been reported previously in a few patients with cystic fibrosis (CF).¹⁻³ The history and long-term implications of this manifestation, however, have not been reported. We present a series of patients with CF seen during a period of 10 years who experienced purpura of the lower extremities associated with increased serum gammaglobulin levels.

METHODS

We reviewed the records of patients with CF treated at St Christopher's Hospital for Children, Philadelphia, Pa, between 1977 and 1987. The diagnosis of CF had been made in all patients on the basis of a typical clinical picture and confirmed by the finding of increased concentrations of sweat electrolytes.

Patients were included in the series if they had a petechial or purpuric rash. We analyzed data obtained at the onset of the rash. These included age and pulmonary function test results as well as hematologic, immunologic, and available skin biopsy results.

The clinical, physical examination, and nutrition components of the original Shwach-

man-Kulczycki system⁴ were recorded. Roentgenograms were scored using the roentgenographic scoring system of Brasfield et al.⁵ Each individual received a maximum of 25 points for each of the four categories to a maximum of 100 points. Demerit points were subtracted to a minimum score of 5 points per category for maximum compromise. In patients who had died, survival after appearance of the rash was calculated.

RESULTS

Sixteen of approximately 500 patients with CF seen from 1977 to 1987 experienced purpura of the legs and feet. The group comprised 8 male and 8 female patients. All patients had *Pseudomonas* species in their respiratory secretions and were being treated with antibiotics, chest physical therapy, and aerosolized mucolytic or bronchodilator drugs. Fourteen patients (78%) were receiving pancreatic enzymes.

The mean age at onset of the rash was 20 years 3 months (range, 9 years 8 months to 33 years 5 months). The mean score at the time the rash was present was 55 (range, 30 to 78). Pulmonary function measurements were abnormal in all patients and ranged in severity from moderately obstructive to severely obstructive-restrictive patterns.

Raised, palpable petechial lesions appeared below the knee and were most prominent over the dorsa of the feet, ankles, and tibial surfaces (Fig 1). In three patients the rash was also present on the soles of the feet. The rash appeared suddenly, frequently associated with pruritus and a burning sensation and slight edema of the feet. It faded spontaneously in 3 to 7 days. The eruption seemed to follow prolonged standing and use of tight garments, such as socks or leather straps of ladies' shoes. Cold temperature did not bring on or affect the rash.

Patients were occasionally treated with nonsteroidal anti-inflammatory

and antihistaminic drugs to relieve pain and pruritus. This therapy did not appear to modify the duration of the rash or its intensity. Corticosteroids were not used. All but four patients experienced multiple recurrences and, eventually, a diffuse purple-brown pigmentation of the affected areas developed (presumably from repeated extravasation of blood into the skin). Five patients (28%) had concomitant arthritis at the onset of the rash. One individual had acute manifestations of hypertrophic osteoarthropathy, with knee and ankle effusions and periosteal elevation.

In six patients (38%) a skin biopsy specimen was obtained. Microscopic examination of the lesion (Fig 2) showed a variable degree of vasculitis and perivascular infiltrate involving mainly the capillaries and venules of the papillary dermis. No immunoglobulin deposits were detected in the three cases in which immunofluorescence techniques were used.

The mean white blood cell count was $10.9 \times 10^9/L$ (range, $5.8 \times 10^9/L$ to $19.3 \times 10^9/L$). Leukocytosis was present only in those patients who had pulmonary exacerbations at the time of the eruption. Slight eosinophilia was seen in three individuals (the absolute eosinophil count was between $400 \times 10^6/L$ and $600 \times 10^6/L$). None of the patients was anemic or leukopenic, with the exception of one patient with cirrhosis of the liver, hypersplenism, and repeated variceal bleeding. Excluding this patient, the mean hemoglobin count was 130 g/L (range, 120 to 169 g/L).

In all 12 patients who had quantitative immunoglobulin determinations, IgG was increased beyond the upper limits of the normal range for age (Table). Immunoglobulin A was elevated in 4 patients (33%), and IgM was elevated in 2 patients (16%). Immunoglobulin E levels were normal in all 12 individuals.

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Fig 1.—Purpuric rash of the lower extremity in a patient with cystic fibrosis.

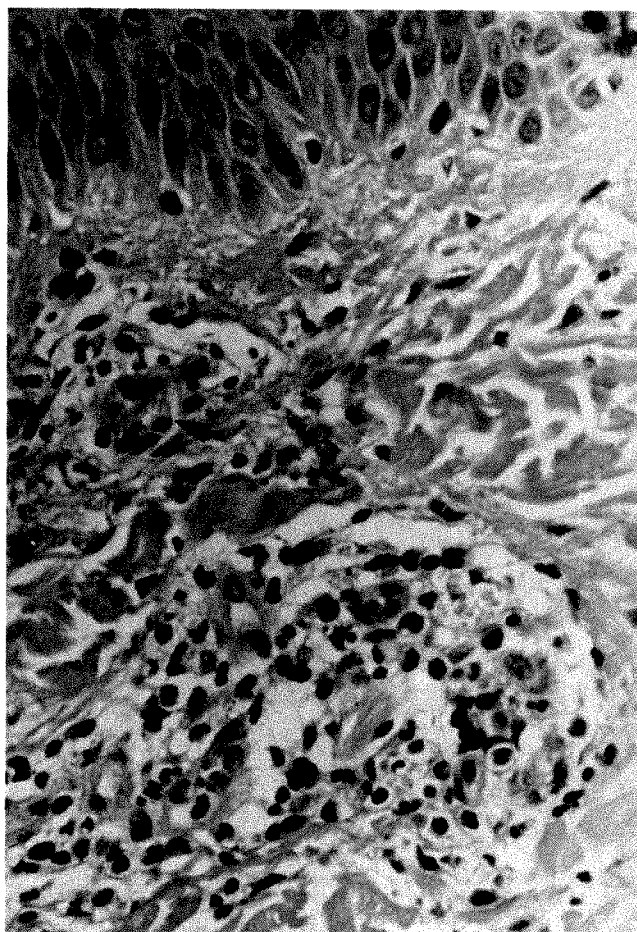


Fig 2.—Skin biopsy specimen of purpuric rash in a patient with cystic fibrosis. Endothelial swelling (arrow) and mixed inflammatory infiltrate within and around small blood vessels is seen in the dermis. There is also focal damage of vessel walls (hematoxylin-eosin, original magnification $\times 100$).

Five (71%) of 7 patients tested had circulating immune complexes (by C1q binding), but none had decreased complement levels.

The diagnosis of Schönlein-Henoch purpura was initially made in one patient based on a mild, transient elevation of the serum urea nitrogen and creatinine concentrations. Results of urinalysis and kidney biopsy were suggestive of this condition. After the renal involvement subsided, the rash recurred several times. All other patients had normal renal function and urine sediment. No patient was hyperuricemic.

At the time of this report, 13 (81%) of the 16 patients had died. The median survival after the appearance of the rash was 16 months (range, 2 to 59 months). The mean and median ages at death were the same: 23 years 3 months

(range, 12 years 5 months to 36 years 1 month).

COMMENT

The characteristics of the skin eruption in our patients with CF are similar to those of hypergammaglobulinemic purpura. This entity was first described by Waldenström⁶ in 1943 and was later reported in four patients with CF by Nielsen et al.⁷ Typically, patients with hypergammaglobulinemic purpura experience recurrent purpuric spots in the lower extremities along with pruritus and a burning sensation in the affected areas. The rash and symptoms are frequently brought on by prolonged orthostatic position. Permanent pigmentation of the skin and polyclonal elevation of circulating gammaglobulins, especially of the G fraction, are also charac-

teristic of this condition. Treatment with anti-inflammatory drugs does not seem to affect the clinical course of hypergammaglobulinemic purpura.⁶

The differential diagnosis includes Schönlein-Henoch purpura; some authors have suggested that Schönlein-Henoch purpura and hypergammaglobulinemic purpura are extremes of the same clinical spectrum, a hitherto unproved hypothesis.⁶ Unlike Schönlein-Henoch purpura, however, hypergammaglobulinemic purpura tends to recur numerous times and can develop in association with collagen vascular diseases.⁶ Purpura, arthritis, and kidney disease have also been described in celiac disease,⁸ bowel-associated dermatosis-arthritis syndrome,⁹ and chronic pulmonary disease¹⁰ with humoral and tissue evidence of immune-mediated damage.

Quantitative Immunoglobulin Levels in Patients With Cystic Fibrosis With Purpuric Rashes

Patient No./ Age at Onset/ Sex	Cystic Fibrosis Score	Immunoglobulin Levels				Biopsy Findings
		IgG, g/L	IgA, g/L	IgM, g/L	IgE, µg/L	
1/20 y 1 mo/M	60
2/22 y 2 mo/F	60	25.00*†	3.60	1.05
3/23 y 10 mo/F	68	25.00*	3.90	1.80
4/20 y 6 mo/F	58	19.00*	5.80*	2.15	103	Perivascular infiltrate and fibrosis
5/25 y 2 mo/M	51	19.00*	2.00	1.80
6/20 y 1 mo/F	50	22.00*†	2.50	2.20
7/18 y 2 mo/M	34	24.40*†	8.00*	3.10	288	Moderate vasculitis
8/22 y 2 mo/F	30	25.00*†	3.90	3.30	...	Mild perivascular infiltrate
9/11 y 4 mo/M	46	†
10/22 y 6 mo/M‡	78	21.80*	6.30*	3.75*
11/14 y 3 mo/F‡	77	17.00*	2.10	1.50	168	...
12/15 y 5 mo/M	75
13/33 y 5 mo/M	36	No vasculitis
14/19 y 4 mo/F	63	26.20*	5.21*	2.43	5.8	Perivascular infiltrate
15/9 y 8 mo/F‡	60	19.70*	3.02	1.85	36.5	Necrotizing vasculitis
16/25 y 11 mo/M	34	21.20*	2.88	7.00*	19.9	...

*Value was greater than the normal range for age in our laboratory.

†Circulating immune complexes were present.

‡The patient was still alive at the time of this report.

It is unlikely that this rash represents a drug reaction. We found no temporal relationship between the administration of specific drugs (such as penicillins) and the onset of purpura. In the absence of specific testing, however, drug hypersensitivity cannot be ruled out with certainty.

Soter et al¹ have previously characterized vasculitic rashes in patients with CF as cutaneous venulitis. Their patients and ours had very similar clinical and laboratory findings.

An exaggerated immune response against bacterial antigens has been

postulated as an important factor in the pathogenesis of tissue damage and inflammation in CF.¹¹ In general, patients with CF with hypergammaglobulinemia have more severe lung involvement and a poorer prognosis than those with normal or low levels of gamma globulin.^{11,12}

The low incidence of purpura in this series is difficult to explain, given the large population of severely ill patients with CF with hypergammaglobulinemia. We were not able to define specific factors that made our patients conspicuously different from similarly ill pa-

tients. A long-term surveillance study would be needed to explore this issue.

In summary, the onset of purpuric rashes of the legs and feet is probably a secondary manifestation of the severity of lung disease in CF. In most patients it is associated with poor long-term survival; thus, it heralds a poor prognosis.

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Dr Panitch was a Cystic Fibrosis Foundation fellow while conducting this study.

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Emergence of Isolates Resistant to Ampicillin

David G. Rupar, MD; Margaret C. Fisher, MD; Hansel Fletcher, MS; Joel Mortensen, PhD

• Clinical isolates of *Streptococcus faecium* demonstrating ampicillin resistance were recovered from eight pediatric patients. Sites of isolation included blood, surgical wound, bile drainage, urine, burns, and peritoneal fluid. Seven patients had prolonged hospitalization, and all had been treated with broad-spectrum antibiotics prior to isolation of the resistant enterococcus. One isolate was from an ill, bacteremic patient; the others were in mixed culture and were not considered causes of disease. The isolates were not epidemiologically related. Minimal inhibitory concentrations for various antibiotics included ampicillin (16 to 32 mg/L), penicillin (128 mg/L), gentamicin (16 mg/L), and vancomycin (2 mg/L). Three isolates demonstrated high-level resistance (>2000 mg/L) to streptomycin; none did so to gentamicin. In vitro synergy testing performed on seven available isolates for ampicillin and gentamicin demonstrated no synergy to this combination. None produced β -lactamase. Combined antibiogram and plasmid data showed at least five distinct patterns. These strains present a new clinical problem in their high level of resistance to ampicillin and to the combination of ampicillin and gentamicin. (AJDC. 1989;143:1033-1037)

Enterococci are constituents of normal bowel flora and are important causes of nosocomial infections. The incidence of nosocomial infections due to enterococci is increasing.¹ Enterococci account for approximately 10% of endemic hospital-acquired infections,^{2,3} making them the third most common cause of nosocomial infections. Occasionally, enterococci cause epidemics in

the hospital setting.^{4,5} Two species, *Streptococcus faecalis* and *Streptococcus faecium*, are primarily responsible for human disease; of these, *S. faecalis* is by far the more common.⁶

Enterococci are generally considered to be of low pathogenic potential, yet many types of infection, including endocarditis, urinary tract infection, and surgical and burn wound infection, are caused by enterococci. Polymicrobial infections are common.^{7,8} Bacteremia results from a focal infection or arises spontaneously, and is attended by significant morbidity and mortality.⁹ In pediatrics, enterococci have achieved prominence as a cause of neonatal septicemia and meningitis.^{5,10,11} Hemming et al¹² reported that enterococci were the second most common cause of nosocomial bacteremia in the neonatal intensive care unit, occurring less commonly than *Escherichia coli* but with equal frequency as *Staphylococcus aureus*. At our institution, enterococcal infection accounts for 7% of nosocomial bacteremia and is frequently related to the use of intravascular catheters.¹³

Between December 1986 and March 1988, eight enterococcal isolates exhibiting an unusual degree of ampicillin resistance were identified by the Clinical Microbiology Laboratory at St Christopher's Hospital for Children, Philadelphia, Pa. The organisms were studied further to define susceptibilities, plasmid patterns, and presence of β -lactamase. Medical records of the patients colonized by these strains were reviewed.

METHODS

Organisms were identified as enterococci by growth on 4% bile and 6% sodium chloride and by esculin hydrolysis. Speciation was performed by a commercially available identification system (Rapid Strep, API Analytab Products, Plainview, NY). Standard disk diffusion susceptibility testing was performed on each isolate. Strains displaying an

absence of any zone of inhibition around a 10- μ g disk of ampicillin were studied further. Minimal inhibitory concentration (MIC) was measured by a commercial antibiotic sensitivity system (American Micro Scan, Baxter Healthcare Corporation, Edison, NJ).

Seven of eight strains were available for further study. American Type Culture Collection strain 29212 (*S. faecalis*) was used as a control in all experiments. Minimal inhibitory concentrations for ampicillin and gentamicin were determined by the broth microdilution method, using serial two-fold dilution of the antimicrobial agent in Mueller-Hinton broth (Difco Laboratories, Detroit, Mich). The MIC was defined as the lowest concentration of the agent at which there was no visible growth after 18 hours' incubation at 37°C. Synergy between ampicillin and gentamicin was determined by the checkerboard microdilution method.¹⁴ The range of final ampicillin concentrations was 0.25 to 128 mg/L, and that of gentamicin was 0.5 to 32 mg/L. Each well was inoculated with organisms to give turbidity equivalent to a final concentration of 5×10^5 organisms per milliliter. The fractional inhibitory concentration (FIC) index was defined as (MIC A combined/MIC A alone) + (MIC B combined/MIC B alone), where MIC A and MIC B represent MICs for the two antibiotics, each measured alone and combined with the other.

Synergy was considered present when the FIC index was less than or equal to 0.5. β -Lactamase activity was tested using nitrocefin disks (Cefinase, BBL Microbiology Systems, Cockeysville, Md) and a plate acidometric method. Cultures were tested in both stationary and logarithmic phases of growth.

Whole-cell DNA was isolated and characterized by standard methods.¹⁵ Briefly, cell lysates were treated with sodium dodecyl sulfate and the DNA was spooled onto a glass rod. Solutions of DNA were electrophoresed on a horizontal gel apparatus (Model HE 99, Hoefer Scientific Instruments, San Francisco, Calif) in a 0.7% agarose gel and stained with ethidium bromide solution.

Patient information was obtained by review of medical records. Epidemiologic data obtained included dates of hospitalization, nursing unit and room, attending physician, resident physician, consulting physicians,

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ancillary hospital services used, surgical procedures, and antimicrobials administered.

RESULTS

Patient information is summarized in Table 1. Ampicillin-resistant enterococci (ARE) were cultured from seven patients between December 1986 and December 1987; the blood isolate was obtained in March 1988. Patients were not related by date of hospitalization, room number, nursing unit, physician caregivers, or ancillary hospital services utilized (ie, respiratory care, physical therapy, etc).

Patients 1 through 7 had serious underlying diseases that placed them at risk for nosocomial infection. Patient 2 was receiving immunosuppressive therapy. Patients 1, 2, 5, 6, and 7 were in the hospital a mean of 14 days (range, 8 to 30 days) preceding the isolation of ARE. Patients 3 and 4 had been readmitted after recent prolonged hospitalizations. These seven patients had received multiple courses of antibiotics in the month prior to isolation of ARE. All were treated with β -lactams, including ampicillin sodium (n=4), nafcillin sodium (n=2), methicillin sodium (n=1), and third-generation cephalosporins (n=3). Six had received an aminoglycoside antibiotic, either gentamicin sulfate or tobramycin sulfate. These seven pa-

tients, although chronically ill, did not show evidence of acute infectious illness. Only three of the patients were febrile, and two of these had alternate explanations for the fever. Specimens from patients 2, 4, 5, and 7 were obtained from superficial sites. These were taken as "surveillance" cultures from patients with minimal erythema or drainage but no evidence of cellulitis or "wound sepsis." The isolate from pa-

tient 1, a child with bilateral ureterostomies, was recovered from a urine sample obtained as follow-up after a urinary tract infection. The colony count was less than 100 colony-forming units/mL and urinalysis was unremarkable. The ARE isolate from patient 6 was obtained from a culture of ascitic fluid obtained at the time of splenectomy; the patient did not have peritonitis. The remaining isolate was obtained from aspi-

Table 1.—Patient Characteristics

Patient No./Age	Time in Hospital, d*	Primary Diagnoses	Surgical Procedures†	Drains or Catheters‡	Multiple Antibiotics§
1/5 mo	8	Prune belly	—	+	+
2/5 mo	10	Renal anomalies	+	+	+
3/3½ y	0	Congenital neutropenia	—	—	+
4/9 mo	3	Biliary atresia	—	+	+
5/8 d	8	Myelomeningocele; hydrocephalus	+	+	+
6/2 y	16	Malignant lymphohistiocytic disorder; multiple organ failure	+	—	+
7/6 y	30	80% body surface area burns	+	—	+
8/3 wk	0	Wound infection with bacteremia	—	—	+

*Time was measured from admission to isolation of resistant enterococci.

†Plus sign indicates surgical procedures associated by time or site with isolation of enterococci.

‡Plus sign indicates patient had indwelling vascular catheter or surgical drain at site of isolate.

§Plus sign indicates several courses of combined antibiotic therapy, including β -lactams, preceded isolation of resistant enterococci.

Table 2.—Microbiological Characteristics of Enterococcal Isolates*

Patient No.	Culture Source	Associated Organisms	Enterococcal MIC, mg/L					β -Lactamase Present	FIC (Synergy)
			Ap	Te	Sm	Gm	Van		
1	Bladder irrigation fluid	<i>Escherichia coli</i>	32	16	>2000	<2000	≤2	No	2.0 (No)
2	Suprapubic drain site	<i>Pseudomonas aeruginosa</i> ; CNS	32	16	>2000	<2000	≤2	No	2.0 (No)
3	Cellulitis aspirate	<i>P aeruginosa</i>	32	≤1	<2000	<2000	≤2	No	2.0 (No)
4	Biliostomy drainage	<i>Klebsiella oxytoca</i> ; <i>E coli</i>	32	16	<2000	<2000	≤2	No	2.0 (No)
5	Intravascular catheter site	<i>K oxytoca</i> ; CNS	32	16	>2000	<2000	≤0.5	No	2.0 (No)
6	Peritoneal fluid	CNS	>16	16	<2000	<2000	<2
7	Burn wound	CNS; <i>P aeruginosa</i>	32	>16	<2000	...	≤0.5	No	5.0 (No)
8	Wound	<i>Enterobacter cloacae</i>	32	...	<2000	No	3.0 (No)
	Blood	None

*MIC indicates minimal inhibitory concentration; Ap, ampicillin; Te, tetracycline; Sm, streptomycin; Gm, gentamicin; Van, vancomycin; FIC, fractional inhibitory concentration; and CNS, coagulase-negative staphylococci.

rate of an area of cellulitis. None of these seven patients received specific therapy for the enterococcal isolate. Patient 6 died 2 days after ARE was recovered; infection was not the major cause of death.

Patient 8 was a 3-week-old neonate who was hospitalized because of fever, irritability, and an infected scalp wound. This neonate had received 2 days of therapy with ampicillin and gentamicin in the first week of life because of fever. No focus of infection was detected, antibiotics were discontinued, and he was discharged in apparently good health. On rehospitalization, he was treated with ampicillin, gentamicin, and vancomycin hydrochloride, and he improved rapidly. Enterococci were recovered from blood obtained at the time of admission. Ampicillin and gentamicin were discontinued, and vancomycin

therapy was given for 10 days.

All ARE isolates were identified as *S faecium*. The blood isolate was a pure culture; all others were found in mixed culture. Associated organisms isolated included coagulase-negative staphylococci, *Pseudomonas aeruginosa*, *Klebsiella oxytoca*, *E coli*, and yeast.

Antibiotic susceptibility data are shown in Table 2. Isolates in patients 1 through 5 and 7 each demonstrated an ampicillin MIC of 32 mg/L; the isolate in patient 8 had an MIC of 16 mg/L. The one strain that was not available for further testing (from patient 6) had an ampicillin MIC of greater than 16 mg/L but less than or equal to 128 mg/L on the commercial MIC panel. No isolate produced detectable β -lactamase. Three isolates demonstrated high-level resistance to streptomycin, but none did so to gentamicin. Comparison of antibiotic

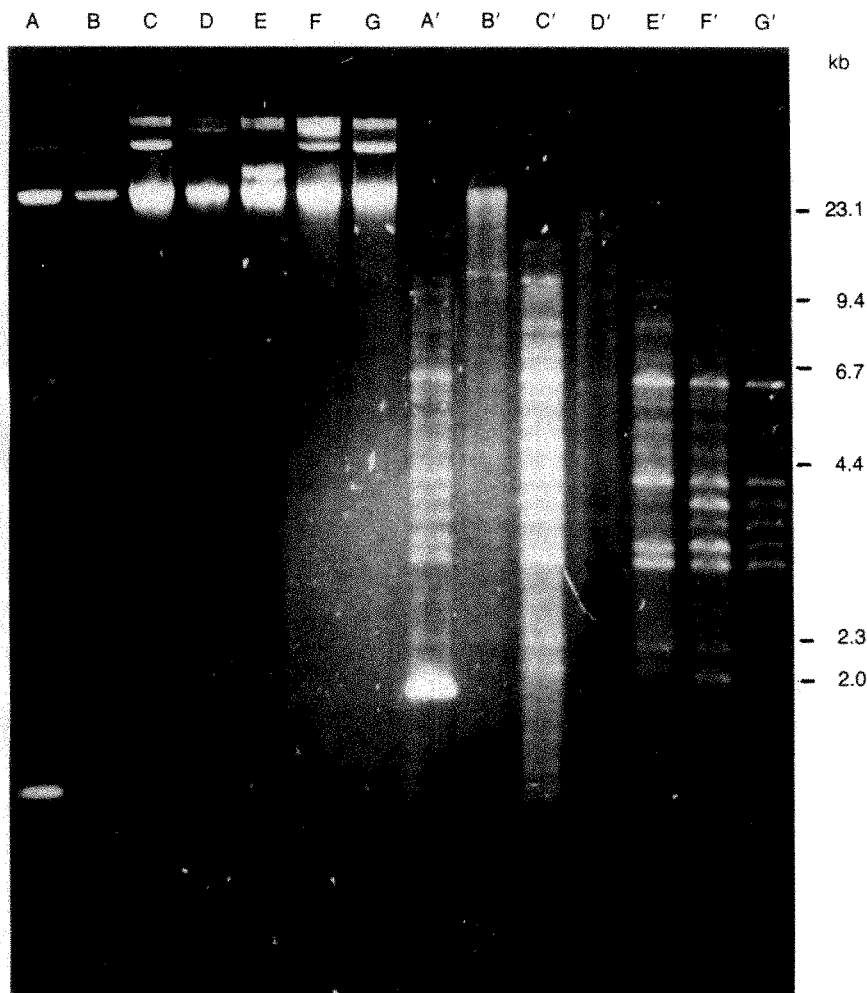
susceptibilities to streptomycin and tetracycline showed three distinct antibiograms. Despite the lack of high-level resistance to gentamicin, all strains had FIC indexes of at least 2.0, indicating no synergy between ampicillin and gentamicin. The control strain, by contrast, had an FIC index of 0.25. Strains from patients 7 and 8 had FIC indexes of greater than 2.0, suggesting antibiotic antagonism.

A review of 75 random isolates of enterococci obtained before the appearance of the ARE at St Christopher's Hospital for Children showed none to be resistant to ampicillin by disk diffusion susceptibility testing.

Plasmid preparations are shown in the Figure. All strains demonstrate a large plasmid (>20 kilobase pairs). The strain from patient 1 (lane A) shows a small plasmid not present in the other strains. A restriction endonuclease, Hind III, digest of the DNA of the strains (lanes A' to G') shows a 1.8-kilobase fragment present only in the strain from patient 1 (lane A'). Strains from patients 2, 3, 5, 7, and 8 (lanes B', C', E', F', and G') show a similar Hind III profile. When all the isolates were probed with a tetracycline-resistant determinant from the transposon Tn916, only the large plasmid of strain from patient 4 (lane D) was homologous (H.F., Laura Marri, MS, Lolita Daneo-Moore, PhD, unpublished data, 1988). Thus, by plasmid analysis there are at least three groups. By analysis of antibiogram (Table 2), strains from patients 2, 3, 5, 7, and 8 have at least three different susceptibility patterns. Therefore, there are at least five different strains represented.

COMMENT

We describe the emergence of high-level resistance to ampicillin in strains of enterococci recovered from eight patients at St Christopher's Hospital for Children. These clinical isolates of *S faecium* have MICs for ampicillin above the published range for this organism. Furthermore, no in vitro synergy of ampicillin and gentamicin could be demonstrated against these strains despite the lack of high-level resistance to gentamicin. The mechanisms for this are not established; preliminary observations



Agarose gel electrophoresis of cellular DNA isolated from clinical isolates of *Streptococcus faecium*. Lanes A through G are isolates from patients 1, 2, 3, 4, 5, 7, and 8. Lanes A' through G' are Hind III digested DNA from the same patients. kb indicates kilobase.

upport the theory that resistance results from alterations in the organisms' penicillin-binding proteins (H.F. and Lolita Daneo-Moore, PhD, unpublished data, 1988). This is consistent with the laboratory observation that gradual increases in antibiotic pressure allow the development of penicillin-resistant enterococci associated with changes in the penicillin-binding protein profile.¹⁶ These isolates were not related epidemiologically. All our patients were at risk for nosocomial infections due to prolonged hospital stay and use of multiple antibiotics. The use of third-generation cephalosporins and aminoglycosides has been associated with enterococcal infections, including those due to high-level aminoglycoside-resistant strains.^{17,18}

The pattern of plasmids suggests that these are several different strains. Antibigrams also varied. This unrelatedness was surprising; we expected to find nosocomial transmission of a single strain with an unusual level of ampicillin resistance. It is likely that each patient acquired the infective strain from his or her own bowel flora, rather than from other patients or hospital personnel.

In the first seven patients, the organisms did not cause infection. The appearance of the bacteremic patient confirmed the potential clinical importance of these organisms. Enterococci have significant pathogenic potential and are major causes of nosocomial infection. *Streptococcus faecium* in particular has been reported as a cause of serious hospital outbreaks of infection in infants.⁵

Enterococci are resistant to a wide variety of antibiotics: cephalosporins of all generations, aminoglycosides, clindamycin, trimethoprim-sulfamethoxazole,

erythromycin, and tetracycline.⁶ Resistance may be intrinsic or acquired via plasmids.¹⁹ The most active agents against enterococci are ampicillin and vancomycin. Even for these, however, enterococci display relative resistance compared with other streptococci. The concentration of ampicillin needed to inhibit 90% of enterococcal strains (MIC₉₀) in published studies is 1 mg/L (range, 0.25 to 4 mg/L),⁶ while the MIC for other streptococci is usually less than 0.1 mg/L. Minimum inhibitory concentrations of penicillin are usually twofold to fourfold higher than those of ampicillin. *Streptococcus faecium* appears to be the more resistant species, with an ampicillin MIC₉₀ of 2 mg/L, and a range from 0.12 to 16 mg/L.²⁰ The mechanism for this "relative resistance" to penicillin and ampicillin in enterococci appears to be the existence of low-affinity penicillin-binding proteins in the cell wall.²¹ Production of β -lactamase, a common bacterial means for penicillin resistance, has not been common among enterococci, though several β -lactamase-producing strains have been reported.²² In general, the susceptibility to penicillins of enterococci has remained stable through the years, with no significant increase noted.^{1,6}

Enterococci demonstrate tolerance to the bactericidal effect of antibiotics acting on the cell wall.^{23,24} Successful therapy of serious enterococcal infections has depended on use of two antibiotics that act synergistically to kill the organism.²⁵⁻²⁷ Aminoglycoside antibiotics, though not active against enterococci at clinically achievable, safe levels, have been found to act in concert with penicillin, ampicillin, or vancomycin to kill the organisms at usual therapeutic

doses.²⁸⁻³⁰ These laboratory observations have been supported by data on experimental endocarditis in animals,³¹ and more importantly by the historical observation that patients with enterococcal endocarditis fared much better when given a combination therapy than a single-agent treatment.³²⁻³³ The strains described in this report do not demonstrate synergy of ampicillin and gentamicin. The child with bacteremia and an infected scalp wound recovered after local drainage of the wound and parenteral therapy with vancomycin.

Vancomycin is the drug of choice for serious enterococcal infections in patients allergic to penicillin. Vancomycin is not bactericidal for enterococci at therapeutic concentrations but does act synergistically with aminoglycosides to kill the organisms.^{29,34} All the isolates in this series were sensitive to vancomycin. However, vancomycin resistance in enterococci has recently been described.^{35,36}

The findings in eight patients colonized by resistant enterococci during a 15-month interval emphasize the importance of routine antibiotic susceptibility testing of all enterococcal isolates. These strains provide yet another example of the ability of microorganisms to adapt to their environment and thwart attempts by modern medical science to combat them. The emergence of ampicillin resistance among enterococci is almost certainly a result of extensive use of antibiotics. The overuse of antibiotics sets the stage for their obsolescence and replacement by more exotic, expensive, and potentially toxic agents.

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Book Review

Migraine in Childhood, edited by Judith M. Hockaday, 158 pp, \$29.95, Butterworth Publishers Inc, Stoneham, Mass, 1988.

Migraine in Childhood, edited by Judith M. Hockaday, MD, of the John Radcliffe Hospital in Oxford, England, is clearly written and clinically useful. The monograph is brief but complete, well organized, and logically presented. The tightness and clarity of the text completely make up for the lack of illustrative figures and the presence of only a few tables. The book reads well, and the work of all eight contributors is skillfully edited and well referenced. It is a welcome addition to the literature on migraine in children.

Dr Hockaday provides a clinically useful definition of migraine, stressing positive criteria, exclusion of other causes, and a mandatory follow-up period. Clinical features and variants are well discussed, with full consideration given to diagnostic limitations. However, the recommendations concerning neuroimaging are vague. The reader is warned not to delay diagnosis of brain tumors and to consider other intracranial and extracranial causes of headache. However, more specific guidelines for computed tomography or magnetic resonance imaging would be helpful.

The neurologic features of migraine are addressed more thoroughly than the gastrointestinal issues. Dr Hockaday clearly points out the difficulties in assigning a diagnosis of abdominal migraine, and provides a useful clinical approach to the problem. However, psychosomatic factors are strongly emphasized as a cause for recurrent abdominal

pain in children, and the differential diagnosis is focused on rarities, such as urea cycle disorders and mitochondrial cytopathy. Guidelines are lacking for consideration of more common causes, such as gastroesophageal reflux, lactose intolerance, constipation, infection with parasites (such as *Giardia lamblia*), or structural abnormalities.

Sensible and helpful advice is provided for the symptomatic treatment of migraine attacks, although one might disagree with the emphasis on metoclopramide as the antiemetic because of its frequent neurologic side effects. In addition, prophylactic treatment for children with frequent, severe attacks is deemphasized to the extent that few specific recommendations are provided. Finally, it should be noted that the recommended dosage of cyproheptadine (30 mg twice daily) is considered high by American standards. For example, the *1989 Physicians' Desk Reference* states that the dosage should not exceed 12 mg/d for children 2 to 6 years of age or 16 mg/d for children 7 to 14 years of age.

Dr Hockaday et al have provided children's physicians with a worthwhile volume on migraine. I agree with the authors that the problem is more common than most doctors realize. Their monograph may help close that gap.

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Anti-*Staphylococcus aureus* IgE Antibodies for Diagnosis of Hyperimmunoglobulinemia E-Recurrent Infection Syndrome in Infancy

Aubert Lavoie, MD; Menachem Rottem, MD; Marshall P. Grodofsky, MD; Steven D. Douglas, MD

• Four infants with hyperimmunoglobulinemia E presented with a persistent papulovesicular rash and eosinophilia. Serum IgE levels and specific anti-*Staphylococcus aureus* IgE antibodies were studied during the first year of life. Increased anti-*S aureus* IgE antibodies were an early indicator of the disease; they appeared as soon as 7 weeks of age in patient 1 and before 1 year of age for the other patients. These antibodies were detected before the development of deeper staphylococcal infections. Prompt diagnosis and treatment are important, as they may prevent long-term infectious complications.

(AJDC. 1989;143:1038-1041)

The hyperimmunoglobulinemia E-recurrent infection syndrome (HIE) is a rare disorder characterized by recurrent severe infections of the skin and sinopulmonary tract, including staphylococcal pneumonias with pneumatocele formation, chronic eczematoid dermatitis, coarse facial features, mild eosinophilia, and markedly elevated serum IgE levels.^{1,2} Although the primary defect is still unknown, a number of immunologic abnormalities have been identified, including the presence of specific antimicrobial IgE antibodies directed against *Staphylococcus aureus* and *Candida albicans*,^{3,4} deficits of salivary total IgA and anti-*S aureus* IgA,⁵ a neutrophil chemotactic defect,^{2,6,7} an abnormal T-cell number and function,⁸ and

impaired antibody responses to carbohydrate and protein antigens.⁹ Our laboratory has developed an assay for IgE antistaphylococcal antibodies that has become a diagnostic test.³ The disease has its onset in infancy, usually within the first 3 months of life.^{2,10,11} Recognition of the syndrome, however, may be difficult in the newborn period, because the clinical features and laboratory studies in the infant have not been well delineated.

We describe four infants who, during the first 2 months of life, had a persistent papulovesicular skin rash, marked eosinophilia, and anemia. The HIE was confirmed when they developed *S aureus* infection, very high levels of serum IgE, and anti-*S aureus* IgE antibodies.

PATIENT REPORTS

PATIENT 1.—A white male neonate was the 4.35-kg product of a 43-week gestation born to a 23-year-old primigravida. Two days after birth, he developed a vesicular rash on the hands and feet. Although Tzanck smears and bacterial and viral cultures from mother and neonate were negative, he received acyclovir and antibiotics for a presumed herpes infection. The only unusual laboratory findings were significant eosinophilia (0.16 of a total leukocyte count of $29.7 \times 10^9/L$) and a hemoglobin level of 109 g/L.

At 7 weeks of age he was hospitalized with fever; his rash had become more diffuse, weeping, and crusted, involving the trunk and scalp. Hepatosplenomegaly and purulent otitis externa were also noted. A skin biopsy revealed a diffuse eosinophilic infiltration of the epidermis with intraepidermal vesicles. Laboratory data are shown in Table 1. Culture from skin lesions yielded *S aureus*, *Enterobacter cloacae*, *Escherichia coli*, and *Klebsiella oxytoca*. Complement level was normal ($CH_{50} = 114$ hemolytic units/mL).

At 8 months of age he was hospitalized for a

S aureus axillary adenitis and treated with surgical drainage and oxacillin. Immunologic tests revealed elevated serum levels of IgE (235 $\mu g/L$ [normal, 0 to 36.5 $\mu g/L$]) and IgG (10.00 g/L [normal, 2.92 to 8.16 g/L]), with normal levels of IgM (1.16 g/L [normal, 0.37 to 1.24 g/L]) and IgA (0.41 g/L [normal, 0.27 to 0.73 g/L]); isohemagglutinins were anti-B 1:32 (blood group A+); and there was delayed neutrophil killing of *S aureus*, with reduced random migration and chemotaxis toward formyl-methionyl-leucyl-phenylalanine relative to control. Nitroblue tetrazolium test results were normal. T-cell subsets (CD3, CD4, CD8) as well as mitogen responses (phytohemagglutinin, concanavalin A, pokeweed mitogen) were normal. Eosinophilia persisted (0.21 eosinophils of a leukocyte count of $18.4 \times 10^9/L$).

At 11 months of age he presented with an *S aureus* right middle- and lower-lobe pneumonia and pleural effusion. Despite intravenous oxacillin therapy, he developed a pneumatocele and a pneumothorax. His IgE levels were above 24 000 $\mu g/L$. Specific antistaphylococcal IgE antibodies were elevated in serum from 7 weeks of age, with 32% binding (normal, <10% binding) and at 8 months of age, with 52.6% binding.

During the following years he continued to have chronic skin infections, repeated otitis media, adenitis, and a pulmonary abscess. Serial values of serum IgE levels and anti-*S aureus* IgE antibodies are shown in Table 2; eosinophil count remained mildly elevated (0.06 of a leukocyte count of $6.2 \times 10^9/L$). He was treated with daily dicloxacillin.

The following two patients are sisters born to a black mother having classic HIE who also has had a brother and a sister afflicted with the same disorder. They have had a typical course of disease, characterized by recurrent staphylococcal pneumonias, some with pneumatocele formation, abscesses, dermatitis, nail changes due to *C albicans* infection, and IgE levels greater than 5000 $\mu g/L$. Specific anti-*S aureus* IgE antibodies were elevated in the mother (18.7% binding) and in the mother's brother (27.1% binding).

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Reprints not available.

Table 1.—Laboratory Findings at the Time of Presentation

Variable	Patient			
	1	2	3	4
Age, wk	7	6	31	52
Hemoglobin, g/L	92	77	97	127
White blood cell count, $\times 10^9/L$	30.4	29.5	16.7	13.4
Eosinophils	0.56	0.20	0.02	0.07
IgG, g/L (normal range, 2.18 to 10.70 g/L)	1.50	3.40	4.43	9.80
IgM, g/L (normal range, 0.11 to 1.13 g/L)	0.70	0.87	0.33	1.16
IgA, g/L (normal range, 0.20 to 1.69 g/L)	0.14	1.18	0.86	1.65
IgE, $\mu g/L$ (normal range, 1 to 24 $\mu g/L$)	163	101	720	3000
Anti- <i>Staphylococcus aureus</i> IgE antibodies, % binding (normal binding, <70%)	32	4.7	0.8	35.4
Chemotaxis	Decreased	Decreased	Normal	...

PATIENT 2.—A black female neonate was the 3.4-kg product of a full-term pregnancy of a 21-year-old woman. At 3 weeks of age she had an upper respiratory tract infection and fever. She was hospitalized and treated with antibiotics despite negative cultures. She had papular and pustular skin lesions over her face (Figure) and a diaper rash. Complete blood cell count revealed a leukocyte count of $27.3 \times 10^9/L$, with 0.15 eosinophils and a hemoglobin level of 127 g/L.

At 6 weeks of age the skin rash had spread to her face, scalp, ears, and back and was oozing and crusted. Coughing persisted with yellowish sputum production. On physical examination, her weight was 3.58 kg (10th percentile) and her height was 54.5 cm (25th percentile). There was evidence of bilateral external otitis; no lymphadenopathy or abscesses were found. Laboratory studies are summarized in Table 1. The chest roentgenogram was normal. She was administered dicloxacillin and gained 0.7 kg over the following week, with significant improvement of her skin rash. Oral candidiasis developed, which was treated with nystatin (Mycostatin). The laboratory studies at 3 months of age revealed a persistent eosinophilia (0.44 of a leukocyte count of $31.5 \times 10^9/L$) with a hemoglobin level of 98 g/L.

At 6 months of age she manifested increased pruritic papulovesicular rash over her face, head, and upper portion of the chest. Her weight was 6.58 kg (25th percentile). She had bilateral otitis and two enlarged cervical nodes. Onychodystrophic changes of the left index finger were noted

and cultures yielded *C albicans*. Neutrophil chemotaxis toward formyl-methionyl-leucyl-phenylalanine and random migration were both markedly decreased. T-cell subsets were CD3, 62% binding (control, 81%); CD4, 44% binding (control, 47%); CD8, 8% binding (control, 27%); and a CD4 to CD8 ratio was 3.4 (control, 1.7). The mitogen responses were normal. Culture of scalp lesions yielded *S aureus* coagulase positive at 40%, as well as group D streptococcus, *Citrobacter*, *Streptococcus pneumoniae*, and *S aureus* coagulase negative. Serial studies of serum IgE levels and anti-*S aureus* IgE antibodies are presented in Table 2. She was treated with prophylactic dicloxacillin.

PATIENT 3.—A black female neonate was the 2.95-kg product of a 22-year-old woman. The pregnancy was complicated by a septic hip joint of the mother during the third trimester. Soon after birth the neonate had pustular lesions on her face. A sepsis workup showed no evidence of infection. One week later, while receiving intravenous antibiotic treatment, the facial eruption worsened and a diaper rash appeared; *S aureus* coagulase positive grew from a small pustule of her skin. Acute otitis media developed, which required a more aggressive antibiotic treatment. Prophylactic oral antistaphylococcal antibiotic therapy was continued.

At the age of 4 months, her weight was 4.5 kg (<5th percentile), her height was 58.5 cm (10th percentile), and her head circumference was 41 cm (51st percentile). The skin was remarkable for an excoriating papular erythematous rash on her face, upper torso,

Table 2.—Total IgE Level and Anti-*Staphylococcus aureus* IgE Antibodies

Patient	Age, mo	IgE Level, $\mu g/L$ *	Anti-bodies, % Binding† Anti- <i>S aureus</i> IgE
1	1 1/4	163	32
	8	235	52.6
	11	24 000	...
	14	...	32
	24	156 000	45
	48	120 000	50.8
2	1/2	101	4.7
	6	19 200	24
	7	6 720	26
	9	11 040	14
	24	12 000	9
3	6	720	0.8
	1	60 000	22
4	12	3000	29.5
	18	3000	35.4
	20	3000	...

*The normal range is 1 to 24 $\mu g/L$.

†The normal binding is less than 10%.



Patient 2. The appearance of facial papular and pustular lesions.

and diaper area. She also had dull tympanic membrane of her right ear and enlarged cervical lymph nodes. Laboratory studies are shown in Table 1. Circulating T- and B-cell numbers were normal.

During the ensuing months the course of her disease was characterized by recurrent otitis media and chronic skin eruption superinfected with *S aureus* and *C albicans*. Ther-

apy consisted of continuous antibiotics and topical treatment. Eosinophil count at 11 months of age was 0.16 of a leukocyte count of $20.2 \times 10^9/L$. Serial serum IgE levels and anti-*S aureus* IgE antibodies are summarized in Table 2.

PATIENT 4.—A white male neonate was the 3.3-kg product of a full-term pregnancy of a 20-year-old primigravida. Since birth he had a chronic papular rash on his face. He developed an eczematous dermatitis in the diaper area resistant to topical antifungal and corticosteroid therapy. In addition, he had recurrent bilateral external otitis. Laboratory findings at 1 year of age are shown in Table 1.

At the age of 18 months, physical examination showed height and weight in the 75th and 95th percentiles, respectively, for his age. He had bilateral purulent discharge from both ears, oral thrush, diffuse erythematous papular rash with excoriations over his face, neck, chest, back, and diaper area, and mild lymphadenopathy.

Serial studies of serum IgE levels and anti-*S aureus* IgE antibodies are shown in Table 2. Complement level was normal (CH_{50} = 110 hemolytic units). Skin tests for delayed-type hypersensitivity (performed toward tetanus, mumps, purified protein derivative, *C albicans*, and trichophyton) showed no reaction. Nitroblue tetrazolium test results were normal; chemotaxis was normal; isohemagglutinins were anti-A 1:32 (blood group B +). Skin biopsy taken from an affected lesion of the chest showed focal infiltrates of histiocytes and eosinophils of the dermis, with extension to the dermal-epidermal interface preserving the epidermis; electron microscopy showed no evidence of Birbeck granules of the Langerhans cell type. Bone survey findings were normal. Sinus films revealed diffuse opacification of the maxillary, ethmoid, and sphenoid sinuses. Chest roentgenogram showed infiltrates in right middle lobe and the adjacent medial basilar segment of right lower lobe. He was treated for his sinusitis and pneumonia. He later developed skin abscesses and recurrent sinusitis, although generally his skin condition improved by local hygiene and long-term use of antibiotics.

COMMENT

We have described four infants who demonstrated the characteristics of HIE: recurrent *S aureus* infections with a predisposition for pneumonia and pneumatocele formation, subcutaneous abscesses, chronic dermatitis, external otitis, adenitis, markedly elevated IgE levels, and eosinophilia.^{2,10,11} All infants manifested an early onset and persistent papulovesicular rash associated

with an exaggerated eosinophilia. Subsequently, they developed typical bacterial infections and markedly increased serum IgE levels. Although the disease develops in early infancy and the clinical features have been previously reported,¹¹ in most of the cases the diagnosis is delayed until childhood. The incomplete clinical picture for infants makes diagnosis difficult. Furthermore, the laboratory findings, including serum IgE levels and anti-*S aureus* IgE antibodies, have not been well studied in young infants; our patients are informative in that respect.

Chronic pruritic dermatitis is a very common manifestation of the syndrome.^{2,10} It is often referred to as an eczematoid rash. In our patients, the skin rash was their first clinical manifestation of the disease and started shortly after birth. Buckley and Sampson,¹¹ in a review of 21 patients, noted that most of their patients had a "history of pruritic dermatitis earlier in life." Similar clinical findings have been mentioned in other articles where the disease was recognized later during childhood.¹²⁻¹⁵ In our infants, the rash consisted of ill-defined papular and pruritic lesions with small superficial pustules and occasionally of superimposed crusted, infected plaques. It involved mainly the face, scalp, neck, and upper portion of the chest. The presence and severity of the dermatitis has recently been associated with elevated urinary histamine, degree of eosinophilia, and antistaphylococcal IgE antibodies.¹⁶

The second noticeable feature of these infants is the striking level of eosinophilia. Peripheral blood eosinophils are known to be decreased at birth and during the immediate postnatal period.¹⁷ The normal eosinophil count in children is approximately $0.24 \times 10^9/L$ (range, 0 to $0.74 \times 10^9/L$).¹⁸ In our fourth patient and in a review of 13 patients with HIE,² all older individuals, the average number of eosinophils was $0.8 \times 10^9/L$ (range, $0.44 \times 10^9/L$ to $1.72 \times 10^9/L$). Patients 1 and 2, younger infants, showed greater eosinophilia, with absolute eosinophil counts as high as $1.42 \times 10^9/L$ (6 weeks of age) and $1.37 \times 10^9/L$ (12 weeks of age), respectively. Patient 3 had a moderate level of eosinophilia.

Additional findings of HIE include

coarse facial features, usually including a broad nasal bridge, prominent nose, and irregularly proportioned cheeks and jaws as well as changes secondary to *C albicans* infection.^{2,10,11} These manifestations were not present in our patients during their first months of life and usually developed later in the course of the disease. On the other hand, nonspecific findings, including anemia and hepatosplenomegaly, probably reflecting a chronic inflammatory state, were part of their initial presentation of symptoms.

The IgE level as well as specific antistaphylococcal IgE antibodies are two characteristic features of HIE^{3,10} and have not been extensively studied in young infants with the syndrome. In most normal infants, umbilical cord blood IgE levels are undetectable ($<1.0 \mu g/L$). After birth, serum IgE levels rise, along with other immunoglobulins, with maximal values appearing between the ages of 10 and 15 years.¹⁹ The IgE level was elevated in our four patients during their first year of life. Patients 1 and 2 had their first measurement done at 6 to 7 weeks of age (163 and 101 $\mu g/L$, respectively); for patients 3 and 4, it was performed at 8 and 12 months of age, respectively, and was 720 and 3000 $\mu g/L$. In the literature there is also a report of a girl, born to a mother with HIE, who had an elevated umbilical cord blood IgE level of 173 $\mu g/L$; she developed the disease during childhood.²⁰ Although diagnostic criteria in the past have used an IgE level at least 10 times greater than normal ($>5000 \mu g/L$),² a child younger than 1 year of age is unlikely to produce such high levels of this immunoglobulin. This is a finding that is also confirmed in infants from atopic families who further develop allergic diseases: 50% of infants have maintained serum IgE levels below 25 $\mu g/L$ until 1 year of age.²¹ In infants with HIE, IgE levels, although usually 10 times greater than normal for age, are still significantly low both in absolute numbers and relative to values in later childhood; serum IgE level above 5000 $\mu g/L$ should not be a requisite in the newborn period.

Elevated levels of circulating anti-*S aureus* IgE antibodies have been well documented in most patients with HIE. In the original report,³ anti-*S aureus*

IgE antibodies were demonstrated in the sera of patients with HIE but were not detected in patients with atopic skin disease, parasitic infections, and chronic or acute staphylococcal infections and in normal individuals. This was confirmed by Berger et al,⁴ who also demonstrated there were specific anti-*C albicans* IgE antibodies, as did two other groups.^{5,8} They all demonstrated the specificity of anti-*S aureus* IgE antibodies for HIE when compared with other conditions associated with increased serum IgE levels with or without recurrent *S aureus* infections. A recent report of 69 patients with atopic dermatitis showed that most patients did not have detectable levels of IgE antibody to *S aureus*.²² However, Abramson et al²³ and Walsh et al²⁴ reported increased anti-*S aureus* IgE antibodies in patients with atopic skin disease but not to the extent of the in-

crease in patients with HIE. In patients 1 and 2, antistaphylococcal IgE antibodies were detected in the sera in the first 6 months of life and were found only at around 12 months of age for patients 3 and 4. This represents an earlier detection of the anti-*S aureus* IgE antibody than reported by Dreskin and Gallin²⁰ in a young girl, where anti-*S aureus* IgE was first found at 2 years of age. The development of anti-*S aureus* IgE antibodies in infants is variable and seems related to the progression of the disease and the occurrence of severe staphylococcal infections, as it was demonstrated in a group of patients with atopic dermatitis in whom there was a direct correlation between anti-*S aureus* IgE levels and *S aureus* counts in the anterior nares.²⁵ The presence of anti-*S aureus* IgE antibodies may serve as a confirmatory test in infancy when the clinical picture of the syndrome as well

as extremely high IgE levels are not yet fully expressed.

In summary, HIE is a complex disorder that has distinctive features in infancy: a recurrent papulovesicular rash and conspicuous eosinophilia before evidence of overwhelming infection. The presence of both elevated serum IgE levels and anti-*S aureus* IgE antibodies is important in confirming the clinical diagnosis in infants. Early recognition of HIE is of therapeutic relevance since use of prophylactic antibiotics is often clinically helpful.

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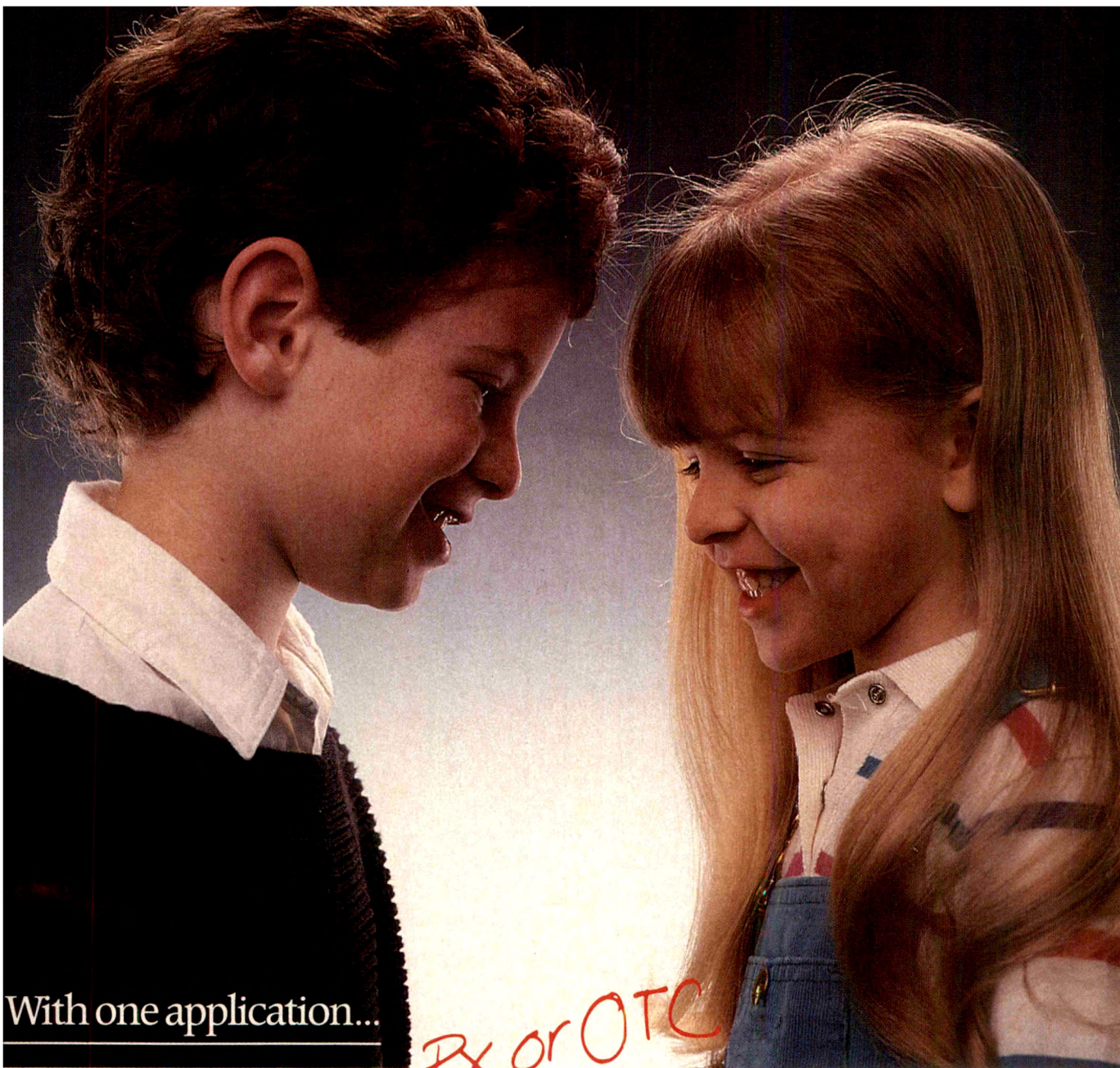
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WARNING: If hypersensitivity to Nix occurs, discontinue use.

PRECAUTIONS:

General: Head lice infestation is often accompanied by pruritus, erythema, and edema. Treatment with Nix may temporarily exacerbate these conditions.

Information for Patients: Patients with head lice should be advised that itching, redness, or swelling of the scalp may occur after application of Nix. If irritation persists, they should consult their physician. Nix is not irritating to the eyes; however, patients should be advised to avoid contact with eyes during application and to flush with water immediately if Nix gets in the eyes. In order to prevent accidental ingestion by children, the remaining contents of Nix should be discarded after use.

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Pregnancy: Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits (200-400 mg/kg/day orally) and have revealed no evidence of impaired fertility or harm to the fetus due to permethrin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the evidence for tumorigenic potential of permethrin in animal studies, consideration should be given to discontinuing nursing temporarily or withholding the drug while the mother is nursing.

Pediatric Use: Nix is safe and effective in children two years of age and older. Safety and effectiveness in children less than two years of age have not been established.

ADVERSE REACTIONS: The most frequent adverse reaction to Nix is pruritus. This is usually a consequence of head lice infestation itself, but may be temporarily aggravated following treatment with Nix. 5.9% of patients in clinical studies experienced mild temporary itching; 3.4% experienced mild transient burning/stinging, tingling, numbness, or scalp discomfort; and 2.1% experienced mild transient erythema, edema, or rash of the scalp.

DOSAGE AND ADMINISTRATION:

Adults and Children: Nix is intended for use after the hair has been washed with shampoo, rinsed with water and towel dried. Apply a sufficient volume of Nix to saturate the hair and scalp (especially behind the ears and on nape of the neck). Nix should remain on the hair for 10 minutes before being rinsed off with water. A single treatment is sufficient to eliminate head lice infestation. Combining of nits is not required for therapeutic efficacy, but may be done for cosmetic reasons or to meet school "no nit" policies. A nit comb is provided.

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Store at 15°-25°C (59°-77°F).

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Treatment of Croup

A Critical Review

Neil S. Skolnik, MD

• Although viral croup is the most common form of airway obstruction in children 6 months to 6 years of age, there is debate regarding medical care for the hospitalized patient. A complete review of the English-language literature from 1960 to 1988 was performed, using both manual and Medline searches. Critical review shows that laryngotracheitis and spasmodic croup, previously emphasized in the literature as having distinct etiologies, most likely are two ends of a broad spectrum in the clinical presentation of a single disease. Critical assessment of all prospective randomized double-blind placebo-controlled trials reported during the study period shows that there is little information on the use of humidified air or supplemental oxygen, that racemic epinephrine hydrochloride is of well-demonstrated efficacy, and that dexamethasone phosphate at a dose greater than 0.3 mg/kg is effective in decreasing the length and severity of respiratory symptoms associated with viral croup.

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Viral croup is the most common form of airway obstruction in children 6 months to 6 years of age. From 1.5% to 15% of children with croup who are seen in an outpatient setting require admission to the hospital, accounting for approximately 20 000 hospital admissions per year in the United States.¹⁻³ During hospitalization, 1% to 5% of children with viral croup require intubation.^{1,3,5}

Although croup is a common illness, there is no consensus about optimal medical management. Mist tents, oxygen, adrenal corticosteroids, and racemic epinephrine hydrochloride are all commonly used treatments. The place and efficacy of these different modal-

ities in the management of croup have been the subject of debate since the early 1960s.^{1,3,6-14} A review of the literature for the last 25 years reveals no single article that critically assesses the efficacy of the various medical treatments of croup. The purpose of this article is to critically review and synthesize the complete body of English-language literature on the medical treatment of croup and formulate a set of recommendations to guide physicians in making treatment decisions for children with croup who require hospitalization. In addition, this article will briefly review the pathophysiological and clinical presentations and differential diagnosis of croup as it relates to treatment decisions; more complete reviews of these areas are available elsewhere.^{1,3,7,9,11}

DATA IDENTIFICATION

A complete review of the English-language literature on the treatment of croup was performed, first by a manual search covering 10 years (1978 to 1988) of the *Index Medicus*, then by reviewing all pertinent references from these articles for the years 1960 to 1988. To ensure completeness of the literature review, this was then checked against a Medline search.

PATHOPHYSIOLOGIC FEATURES

Croup, a syndrome of laryngeal obstruction, is most commonly caused by a viral infection in the subglottic region of the larynx.^{1,3,7,9} The most common virus-causing croup is parainfluenza virus type I. Other less common viral origins include parainfluenza virus types II and III, influenza virus type A, respiratory syncytial virus, and the rhinoviruses.^{1,2,7,9} When the subglottic region of the larynx, held rigidly within the ring of the cricoid cartilage, becomes infected, there is edema of the subglottic region, which leads to narrowing of the

airway. Since the infant's larynx is normally very narrow, a small decrease in the radius of the airway due to edema leads to a large decrease in the area available for air flow. This causes obstruction of air flow, stridor, and shortness of breath.

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

The mean age of children presenting with viral croup is approximately 18 months, with a range from 3 months to 5 years.⁷ Boys are affected more often than girls. There is seasonal occurrence, with a dramatic increase in cases beginning in early autumn and continuing into the winter months.^{2,15} Croup is usually preceded by an upper respiratory tract infection, and as the subglottic region becomes involved, a characteristic "croupy" or barking cough develops. As obstruction progresses, inspiratory stridor develops and becomes associated with flaring of the ala nasi, suprasternal retractions, and intercostal retractions.

Physical examination usually shows a child in minimal to severe respiratory distress, with varying amounts of fever, dyspnea, inspiratory stridor, flaring of the ala nasi, intercostal and suprasternal retractions, and a barking "seal-like" cough. Lungs are usually clear to auscultation, with transmitted upper airway sounds, though there may occasionally be mild wheezing. Laboratory examination reveals a normal or mildly elevated white blood cell count, with white blood cell counts in excess of $15 \times 10^9/L$ occurring in about 20% of patients with croup.¹⁵ Posteroanterior roentgenograms of the neck classically show a narrowed subglottic region with a "steep" sign indicative of subglottic narrowing. On lateral neck roentgenograms there may be a widening of the hypopharynx. Classic signs of croup ap-

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pear on the roentgenogram in only 40% to 50% of cases.^{8,15,16}

The differential diagnosis of croup includes a number of life-threatening illnesses, including epiglottitis, aspiration of a foreign body, and retropharyngeal abscesses. Other diseases to be considered in the differential diagnosis are peritonsillar abscesses, bacterial tracheitis, acquired or congenital subglottic stenosis, infectious mononucleosis, paraquat poisoning, and laryngeal lymphoma. Excellent reviews have been written on the differentiation of croup from epiglottitis.^{1,3,7,9,16}

SPASMODIC CROUP VS LARYNGOTRACHEITIS

The diagnosis of croup has traditionally included the distinction between spasmodic, or recurrent, croup (SC) and laryngotracheitis (LT). Some researchers have felt that this distinction is important because SC may improve rapidly with or without treatment.^{6,8} Though the terms have existed for a long time, there is a paucity of literature to support this distinction. The clinical distinction between SC and LT in the literature is not clear. Spasmodic croup is described as occurring with or without a preceding upper respiratory tract infection, occurring at night, being abrupt in onset, and being generally mild in its course. Laryngotracheitis is described as occurring after a preceding upper respiratory tract infection, occurring at night, having severity that worsens quite rapidly or over a period of hours, and being mild or severe. Both forms of croup occur in children of the same age group and are associated with the same respiratory viruses.^{3,8,17,18}

Some authors have suggested that SC differs from LT in that SC may be an allergic reaction to viral antigens rather than a true infection with the virus as in LT.¹³ Two studies have been used to support this theory, and both have serious flaws. In one, children who had a history of "recurrent croup" had a higher incidence of allergy than children with a history of nonrecurrent croup when studied 9 years after their last admission to the hospital.¹⁹ In the other, children older than 6 years of age, hospitalized with recurrent croup during the previous 12 months, had significantly greater airway hyperreactivity to hista-

mine challenge than a group of healthy controls.²⁰ Both of these studies suggest that children who have an allergic predisposition may have more upper respiratory tract infections or more-severe upper respiratory tract infections, leading to repeated hospitalization, but neither convincingly shows a difference in the cause of SC from that of LT.

Spasmodic croup and LT display a large overlap of symptoms, clinical presentation, and viral origin. The pathophysiology of subglottic edema leading to upper airway obstruction is the same for the two entities.^{8,9} No study has convincingly shown that the underlying causes differ, nor has any study been able to give good, reliable criteria to prospectively separate the two entities.^{13,17-19} Laryngotracheitis and SC most likely are two ends of a broad spectrum in the clinical presentation of a single disease.

TREATMENT

The most important aspects of the treatment of croup are arriving at the correct diagnosis, assessing the severity of the disease, and providing careful observation for deterioration of the hospitalized patient. Once the diagnosis of viral croup has been made, therapeutic options include humidified air, oxygen therapy, racemic epinephrine, and corticosteroids. All of the published studies on the treatment of croup have examined a cohort of patients needing hospitalization due to severe croup; therefore, the recommendations that follow apply only to patients hospitalized with croup, and one must be cautious in generalizing this information to the ambulatory setting.

Humidified Air and Oxygen

Humidified air, with and without supplemental oxygen, is often provided by a mist tent as a routine part of treatment for any child hospitalized with croup. Inhalation of moist air in the treatment of croup has its roots in the late 19th century, when parents found that steam from tea kettles or hot tubs helped break the spasms of croup. This empiric observation led to the use of "croup kettles" in hospitals.³

Humidified air presumably works through two mechanisms. It moistens secretions, making it easier for the child

to bring them up, and it soothes inflamed laryngeal mucosa, making the child feel more comfortable. This may diminish submucosal irritation by helping to decrease the amount of coughing. There are no data showing any effect of humid air on subglottic edema, the main pathophysiologic defect in croup.

Two studies have looked at the effectiveness of moist air in the treatment of croup. One showed no improvement in total respiratory resistance when measured before and after the administration of 2 mL of nebulized sterile water in 5 children.²¹ The other assessed 16 consecutive patients randomly assigned to receive no treatment other than observation in a normal hospital environment (relative humidity, 48% to 52%) or treatment with a mist tent (relative humidity, 87% to 95%). Results showed no benefit of treatment in a mist tent over control when patients were assessed for 12 hours.²²

Henry,²³ in an elegant commentary on the use of humidified air for croup, contends that the improvement seen when a child is held in its mother's arms near a steamy shower may be due as much to the "comfort and reassurance" that the child has in that environment as to the steam. He feels that without evidence to the contrary, separating a child from its parents to put it in a mist tent is more distressing to the child than it is helpful.

The use of oxygen in croup is controversial. In one study that measured arterial blood gas values in children admitted to the hospital with the diagnosis of croup, 29 of 35 children were found to be hypoxemic.²⁴ In these individuals, hypoxemia more closely correlated with respiratory rate, and the degree of observed stridor was an unreliable indicator of hypoxemia. There are a number of possible causes for this observed hypoxemia: (1) direct infection of lung parenchyma with parainfluenza virus, leading to impaired diffusion capacity in the lung; (2) ventilation/perfusion mismatch, secondary to direct infection of lung parenchyma; and (3) pulmonary edema, secondary to the negative intrathoracic pressure occurring during inspiratory airway obstruction.²⁵ There has been no controlled trial of the use of supplemental oxygen in croup, so there are no data on which to make a decision for or against the use of oxygen in a

Table 1.—Double-Blind Randomized Trials of the Use of Epinephrine in the Treatment of Viral Croup*

Source, y	No. of Patients	Dose	Method of Delivery	Significant Effect†	Duration of Effect, h
Fogel et al, ²⁶ 1982	14	0.25 mL of 2.25% racemic epinephrine in 2 mL of NS	IPPB vs nebulizer	+	1
Gardner et al, ²⁶ 1973	20	0.5 mL of 2.25% racemic epinephrine in 3.5 mL of NS	Nebulizer	—	0
Taussig et al ²⁷ 1975	13	0.25 mL of 2.25% racemic epinephrine in 1.5-2.75 mL of NS, depending on weight	IPPB	+ at 10 min, — at 2 h	<2
Westley et al, ²⁶ 1978	20	0.5 mL of 2.25% racemic epinephrine in 3.5 mL of NS	IPPB	+ at 10 and 30 min, — at 2 h	<2
Kuusela and Vesidari, ¹⁷ 1988	78	0.25 mL/5 kg of body weight of 2.25% racemic epinephrine by nebulizer	IPPB	+	...

*NS indicates normal saline solution; IPPB, intermittent positive pressure breathing.

†The effect of epinephrine in the treatment of viral croup had a positive (plus sign) or negative (minus sign) outcome.

clinical setting. Since it is difficult to achieve oxygen concentrations above 40% in a mist tent, oxygen is unlikely to be of any detriment and may be of some theoretical advantage.

In summary, there is no evidence that humidified air or supplemental oxygen is of benefit to children hospitalized with croup. Based on anecdotal evidence, it is prudent to maintain reasonable humidity in the hospital room. This is easily and comfortably provided for by a portable humidifier. Given the large amount of anecdotal evidence, it is not unreasonable to use a mist tent, with or without supplemental oxygen, as long as it is well tolerated by the child.

Racemic Epinephrine

Racemic epinephrine administered by a nebulizer, either with or without intermittent positive pressure breathing, has frequently been used since its introduction by Adair³ in 1971. Racemic epinephrine is believed to work via its α -adrenergic effects. α -Adrenergic stimulation causes mucosal vasoconstriction, leading to decreased edema in the inflamed subglottic region.³

Five prospective studies have evaluated the efficacy of racemic epinephrine in the treatment of croup (Table 1). All five were double-blind placebo-controlled trials that assessed drug effect through scoring systems of clinical variables that reflect airway obstruction. The scoring systems assess level of consciousness, stridor, color, retractions, cyanosis, croupy cough, and dyspnea. Four of the five studies concluded that racemic epinephrine decreases airway

obstruction.^{17,26-28} The only study showing no effect of racemic epinephrine on airway obstruction failed to specify how long after administration of the medication assessment of the patient was carried out.²⁹ As discussed below, it is possible that a transient effect of racemic epinephrine could have been missed if patient assessment was carried out more than 1 to 2 hours after administration of the medication.

Three studies assessed the duration of effect of racemic epinephrine. These studies showed a significant decrease in airway obstruction when measured within 30 minutes of treatment. The degree of obstruction returned to baseline level or above by 2 hours after administration of the medication.²⁶⁻²⁸ Treatment with racemic epinephrine appears to cause a rebound effect in some patients, with the degree of obstruction becoming greater 2 hours after treatment than it was before administration of the drug.

In summary, the evidence from four of five clinical trials supports a strong effect of racemic epinephrine in decreasing airway obstruction from 10 to 30 minutes after administration. This effect wanes over time and disappears by 2 hours after administration, with rebound effects in some cases. Nebulizer rather than intermittent positive pressure breathing is recommended for administration of racemic epinephrine since there is no evidence showing intermittent positive pressure breathing to be superior to nebulization. In addition, nebulization is tolerated better and has less risk than intermittent positive pressure breathing.²⁶

Adrenal Corticosteroids

The efficacy of adrenal corticosteroids in the treatment of croup has been debated since first introduced for croup in the early 1960s. Theoretically, corticosteroids may decrease subglottic edema by suppressing the local inflammatory reaction, by shrinking lymphoid swelling, and by decreasing capillary permeability.^{3,30,31} Twelve studies, from 1960 to 1988, have assessed the efficacy of adrenal corticosteroid use in viral croup. These studies have yielded conflicting results (Table 2).

Tunnessen and Feinstein,⁶ in an analytical review of corticosteroid treatment of viral croup, have pointed out major methodologic problems in studies reported through 1978. They concluded that controversy over the efficacy of corticosteroids in the treatment of croup arises from inadequacies in the performance of three methodologic strategies: (1) establishment of diagnostic criteria for croup, the main problem being the lack of separation of SC from LT; (2) adequacy of corticosteroid dosage; and (3) choice of the outcome event. Tunnessen and Feinstein defined an adequate choice of outcome event to be "Relief in the severity of the obstructive symptoms . . . represented by a reduction in the summation score for severity of signs and symptoms of croup, such as stridor, retractions, cyanosis, and pulse and respiratory rates, rather than changes in individual signs and symptoms."⁶

An inadequate choice of outcome events seems to have been a serious problem in the studies performed be-

Table 2.—Double-Blind Randomized Trials of the Use of Adrenal Corticosteroids in the Treatment of Viral Croup

Source, y	No. of Patients	Study Design*	Dexamethasone Phosphate Equivalent†	Corticosteroid Effect	Decreased Length of Hospital Stay
Martensson et al, ³⁴ 1960	288	P	Approximately 0.05-0.07 mg/kg	+	...
Novik, ³⁶ 1960	208	P	<0.05 mg/kg	—	N
Sussman, ³⁵ 1964	8	P	Calculated likely to be <0.1 mg/kg	—	...
Eden and Larkin, ³³ 1964	47	P	0.18 mg/kg	—	...
Eden et al, ³² 1967	50	P	0.1 mg/kg	—	...
Ross, ³⁷ 1969	263	R	<0.05 mg/kg	—	Y
Skowron et al, ³⁹ 1966	200	P	0.4-0.5 mg/kg	±	Y
James, ¹⁵ 1969	88	P	0.4-0.9 mg/kg	+	N
Leipzig et al, ³⁸ 1979	30	P	0.3 mg/kg	+	Y
Muhlendahl et al, ⁴⁰ 1982	349	P	0.5 mg/kg	+	...
Koren et al, ¹⁸ 1983	78	P	0.6 mg/kg	—	...
Kuusela and Vesidari, ¹⁷ 1988	72	P	0.6 mg/kg	+	Y
Postma et al, ¹⁶ 1984	43	R	0.5 mg/kg	+	...

*P indicates prospective; R, retrospective.

†The effect of corticosteroids in the treatment of viral croup had a positive (plus sign) or negative (minus sign) outcome or both (plus/minus sign).

fore 1969. These same studies all also used inadequate doses of corticosteroids.³²⁻³⁶ The distinction of SC from LT has been discussed extensively in the section above and, as outlined, is unlikely to have contributed to the conflicting results in different studies. The major methodologic strategy that has led to conflicting results among reported clinical trials is the use of differing doses of corticosteroids.

Six studies have used a dose of corticosteroids less than 0.2 mg/kg of dexamethasone phosphate or its equivalent.³²⁻³⁷ While these studies do have methodologic flaws,⁶ five of them showed that corticosteroids have no effect on outcome (Table 2).

Six studies have used a dose of corticosteroids greater than 0.3 mg/kg of dexamethasone phosphate or its equivalent.^{15,17,18,38-40} To assess the efficacy of corticosteroid treatment, it is this group of studies that is best examined. Each of these six studies was a prospective randomized double-blind trial and, with one exception,¹⁸ used well-defined clinical scoring systems, rating levels of stridor, retractions, tachycardia, dyspnea, cyanosis, and respiratory rate to

define outcome. Four of these six studies showed a significant beneficial effect of corticosteroids when compared with placebo.^{15,17,38,40} The two studies that did not report a significant beneficial effect of an adequate dose of corticosteroids deserve further comment.

The study by Skowron et al,³⁹ which concluded that corticosteroids provide no significant benefit in the treatment of croup, showed a strong trend in favor of a beneficial effect. Corticosteroids were shown to be significantly more effective than placebo in four of seven clinical parameters measured. In the other three parameters measured there was a strong trend, not reaching significance, in favor of corticosteroid use.

The only study that has used a dose of dexamethasone phosphate greater than 0.3 mg/kg that does not support the effectiveness of corticosteroids has two major methodologic deficiencies.¹⁸ First, all patients enrolled in this trial were given chloral hydrate at a dose of 75 mg/kg. The use of sedative medication is not a usual or accepted mode of treatment for patients in respiratory distress, and it is not known how sedatives affect outcome and evaluation of

patients with croup. Second, respiratory rate, measured for 6 hours, was the only parameter monitored to assess patient response. Respiratory rate is not as sensitive an indicator of upper airway obstruction as are the summation scores of respiratory distress that were used in the other six studies that used an adequate dose of corticosteroids. In addition, a dose of corticosteroids administered on admission does not reach maximum effect until 6 hours later.⁸¹ Most studies that have documented a response to corticosteroid administration have shown that clinical status improves over a 12- to 24-hour period,^{15,38} though the study by Kuusela and Vesidari¹⁷ showed a significant difference at 6 hours after administration.

In summary, four of six prospective randomized trials using an adequate dose of adrenal corticosteroids showed a statistically significant benefit of corticosteroids in decreasing the length and severity of respiratory symptoms when compared with placebo in the treatment of viral croup. One of the two trials that did not show a significant difference between corticosteroids and placebo showed a strong trend in favor of a bene-

ficial effect of corticosteroids. The only study that did not show corticosteroids to be effective in croup had serious methodologic flaws.

Four prospective trials using an adequate dose of corticosteroids have assessed length of hospital stay. Three of these studies showed a decrease in length of stay for children treated with corticosteroids.^{15,17,38,39} The efficacy of repeated doses of corticosteroids has not been examined in any study. Since the adverse effect of a short course of corticosteroids is very small^{20,41} and no study of corticosteroid use in croup has reported any adverse effects related to corticosteroid use, it seems that the evidence is overwhelmingly in favor of recommending intramuscular administration of dexamethasone phosphate in a dose of 0.6 mg/kg to be given on admission to any child admitted to the hospital with a diagnosis of viral croup. This is consistent with a recent meta-analysis of randomized trials assessing the use of corticosteroids in viral croup.⁴²

Antibiotics

Viruses are the causative agent in most cases of infectious croup.^{1,3,7,9} Once a careful diagnostic workup is completed and causes other than viral croup, including epiglottitis, bacterial tracheitis, and retropharyngeal abscess, are ruled out, there is no evidence that antibiotics are of any benefit in the treatment of viral croup; nonetheless, antibiotics continue to be used. In a retrospective chart review preformed in North Carolina from 1977 to 1981, 58% of patients admitted with a diagnosis of croup received antibiotics, usually ampicillin sodium.¹⁶

In the absence of other aspects of the clinical picture that suggest a bacterial process, there is no reason to use antibiotics in the treatment of hospitalized patients with infectious croup.

CONCLUSION

A rational approach to the treatment of the child with severe croup requiring hospitalization is to use a combination of humidified air, racemic epinephrine, and adrenal corticosteroids, all given under careful observation. Humidified air, though not of proved benefit, may be provided by a mist tent, with or without oxygen, or by a humidifier placed in the child's room. Racemic epinephrine,

administered by nebulizer in a dose of 0.25 mL of 2.25% racemic epinephrine hydrochloride in 2 to 3 mL of normal saline solution, given on admission and then every 2 hours as needed, has well-established efficacy and can help to decrease the degree of laryngeal obstruction during the early hours of admission, before the corticosteroids have begun to take effect. Dexamethasone phosphate, 0.6 mg/kg given intramuscularly on admission, is well supported in the literature to be effective in the treatment of obstructive airway symptoms due to croup, and there is some suggestion that it may decrease length of hospital stay.

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Corticosteroids as Adjunctive Therapy in Bacterial Meningitis

A Meta-analysis of Clinical Trials

Peter L. Havens, MD, MS; Karen J. Wendelberger, MD; George M. Hoffman, MD; Martha B. Lee, PhD; Michael J. Chusid, MD

• A meta-analysis of all nine available controlled trials of corticosteroids for adjunctive therapy for bacterial meningitis was performed. Risks of various outcomes were assessed for control and treatment groups from each study, and risk differences were determined. For each outcome a weighted average of the individual risk differences was calculated. The results show that corticosteroid administration did not reduce the risk of death or neurologic abnormality at hospital discharge or follow-up examination. Based on statistically combined results of the three most recent trials, there is evidence that dexamethasone reduces the risk of bilateral moderate or more severe hearing loss (risk difference, -9%; 95% confidence limits, -15% and -3%). However, this may be true only for children with meningitis caused by *Haemophilus influenzae* type b. There are inadequate data in adults or in children with meningitis due to other organisms to demonstrate the benefit of dexamethasone administration. Further study is necessary to fully assess the benefits and risks of corticosteroids for adjunctive therapy for bacterial meningitis.

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Acute bacterial meningitis remains a potentially devastating illness. Despite improvements in antimicrobial chemotherapy and supportive patient care, the case fatality rate remains 1% to 8%.¹⁻⁵ The rate of serious neurologic sequelae is 10% to 30%,⁶⁻¹² and the rate of hearing loss is 5% to 31%.^{10,11,13-16}

Corticosteroids have been employed as adjunctive treatment of bacterial

meningitis in the hope of reducing the rates of hearing loss and other neurologic sequelae.¹⁷⁻³⁰ While results of one recently published study suggest that corticosteroid therapy may reduce hearing loss following acute bacterial meningitis,²⁹ other studies have demonstrated no benefit^{25,26,28,30} or have suggested that in patients treated with corticosteroids, the outcome is worse than in control patients.^{18,24}

When there are multiple studies with conflicting results, therapeutic decisions can be difficult to make. Meta-analysis, "the statistical analysis of a collection of analytic results for the purpose of integrating the findings,"³¹ offers useful techniques to approach this problem.^{32,33} We have used meta-analysis to evaluate the efficacy of corticosteroids in acute bacterial meningitis by pooling the results of the available controlled clinical trials.

MATERIALS AND METHODS

To obtain reports of the use of corticosteroids in treatment of acute bacterial meningitis, we performed a computer search of the English-language literature from 1966 through 1988 using Medline. We also reviewed the bibliographies of the articles obtained by the computer search as well as the bibliographies of reviews of the therapy for bacterial meningitis.³⁴⁻³⁸

All studies were reviewed by all of us. Only randomized, concurrently controlled trials were included in the meta-analysis. Data were abstracted in a blind fashion by three of us (K.J.W., G.M.H., and M.J.C.), and discrepancies in evaluation were resolved by group consensus. Data regarding the following end points were sought from each study: death, definite neurologic abnormality at discharge and at follow-up examination, and hearing loss at follow-up examination.

For each trial the risk of each specific outcome was calculated as the proportion of af-

fected individuals in treatment or control groups. The risk difference (RD, risk in the treatment group minus risk in the control group) was calculated for each outcome in each study.³⁹ When RD is calculated in this fashion, a negative value suggests treatment benefit. Ninety-five percent confidence limits (CLs) were calculated for all proportions.³⁹ When the 95% CLs of the RD include 0, no statistically significant difference exists.

The results of all the trials were combined by two different methods. First, for each outcome the number affected and group totals were summed, and the RD was calculated from that simple sum. In addition, the RDs were combined using the method of DerSimonian and Laird⁴¹ to give a "weighted average" RD and variance. This method gives less weight to studies with larger variances and to studies with RDs further from the mean of the others. Since only studies with similar methods were combined, a test for homogeneity of the RDs was not performed.³²

We combined all reports with data available on each outcome. We also analyzed the subgroup of five studies that were performed primarily in children.^{24,25,29,30} This separates the "pediatric studies" from three studies carried out primarily in adults^{18,21,28} and one study restricted to adults and children with meningitis caused by *Streptococcus pneumoniae*.²⁶

RESULTS

Fourteen reports of corticosteroid use in acute bacterial meningitis in human subjects were found. Uncontrolled^{17,19,22,27} or retrospective²³ series were excluded. One series²⁰ was excluded because it duplicated a previous report.¹⁸ One report²⁸ included results of two different trials, each of which is considered separately. Not all reports contained data regarding all of the end points of interest; these deficiencies are reflected in the tables and figures.

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Table 1.—Details of Nine Clinical Trials That Used Corticosteroids as Adjunctive Therapy for Bacterial Meningitis

Source, y	Age Range	Group Assignment	Placebo	Double Blind	Antibiotics Used, by Causative Agent (No. of Patients With Organism)*			Corticosteroid Dosage
					<i>Haemophilus influenzae</i> Type b	<i>Streptococcus pneumoniae</i>	<i>Neisseria meningitidis</i>	
Lepper and Spies, ¹⁸ before 1958	All ages	Alternate	No	No	Tetracycline or oxytetracycline, chloramphenicol (57)	Penicillin G, penicillin G and streptomycin (23)	Sulfonamide, tetracycline (49)	Hydrocortisone, 2.5 mg/kg per 24 h, 250 mg/d for 5 d; corticotropin, 100 mg/d intramuscularly on days 6 and 7
Cooperative Study Group, ²¹ 1959-1962	>16 y	Random	Yes	Yes	Not applicable (0)	Not stated (56)	Not stated (9)	Hydrocortisone, 300 mg on day 1, decreasing by 50 mg daily over 6 d
DeLemos and Haggerty, ²⁴ 1960-1964	Children >1 mo	Random	Yes	Yes	Chloramphenicol (69)	Sodium sulfadiazine, penicillin G (13)	Sulfadiazine (16)	Methylprednisolone, 40 mg every 6 h for 3 d
Belsey et al, ²⁵ 1963-1964	Children	Random	Yes	Yes	Chloramphenicol and sodium sulfadiazine (54)	Penicillin G potassium and sodium sulfadiazine (6)	Penicillin G potassium and sodium sulfadiazine (22)	Dexamethasone, 1.2 mg/m ² every 6 h for 4 d
Jensen et al, ²⁶ 1961-1965	>1 mo	Date of birth (odd/even)	No	No	(0)	Penicillin G and sulfadiazine (81)	(0)	Hydrocortisone, 100 mg intramuscularly; prednisolone, 10 mg by mouth 4 times per day for 7 d
Bademosi and Osuntokun, ²⁸ 1979	>10 y	Random	No	No	(0)	Penicillin G and sulfadiazine (52)	(0)	Hydrocortisone, 100 mg intravenously; prednisolone, 60 mg/d by mouth for 14 d
Lebel et al (group 1), ²⁹ 1984-1985	Children >2 mo	Random	Yes	Yes	Cefuroxime sodium (77)	Cefuroxime sodium (18)	Cefuroxime sodium (7)	Dexamethasone, 0.6 mg/kg/day every 6 hrs for 4 d
Lebel et al (group 2), ²⁹ 1986-1987	Children >2 mo	Random	Yes	Yes	Ceftriaxone sodium (77)	Ceftriaxone sodium (7)	Ceftriaxone sodium (10)	Dexamethasone, 0.6 mg/kg per day every 6 h for 4 d
Lebel et al (group 3), ³⁰ 1987-1988	Children >3 mo	Random	Yes	Yes	Cefuroxime sodium (45)	Cefuroxime sodium (9)	Cefuroxime sodium (4)	Dexamethasone, 0.6 mg/kg per day every 6 h for 4 d
Total	(379)	(257)	(117)	...

*The sum (753 patients) is lower than the total number of patients in the studies because some patients had other organisms cultured or had sterile spinal fluid.

Table 1 shows the specifics of the nine clinical trials that were included in the meta-analysis.^{18,21,24-26,28-30} Assignment to treatment or control group was random in seven, by date of birth in one, and by alternate patient in one. Six of the studies were blind and placebo-controlled. The corticosteroid dosage used was variable, as shown in Table 1. The lowest dosage given was equivalent to 2.5 mg of hydrocortisone per kilogram daily¹⁸; the highest dosage was equivalent to 15 mg of hydrocortisone per kilogram daily.^{29,30} The studies included a total of 846 patients with meningitis: 379 (45%) with *Haemophilus influenzae* type b, 257 (30%) with *S pneumoniae*, 17 (14%) with *Neisseria meningitidis*, and 93 (11%) with other, undetermined, or unstated causal agents. For the 470 patients in the studies performed pri-

marily in children,^{24,25,29,30} the causative organisms were as follows: 322 (69%) with *H influenzae* type b, 45 (10%) with *S pneumoniae*, 59 (13%) with *N meningitidis*, and 44 (9%) with other, undetermined, or unstated organisms.

The mortality rate was not changed by corticosteroid use. One study excluded patients who died.³⁶ In the eight remaining studies, the median case fatality rate was 4.5% in the corticosteroid-treated group and 2% in the control group. The RD for death varied from -16% to 18%. When the risk differences from these eight studies were combined,³¹ the weighted average RD was 0.9% (95% CLs, -2% and 4%). For the pediatric studies, the weighted average RD was 0.1% (95% CLs, -3% and 3%).

The percentage of individuals with a

definite neurologic abnormality evident at the time of hospital discharge was significantly decreased in corticosteroid-treated patients in one study (RD = -17%; 95% CLs, -32% and -2%).²⁹ Conversely, another study¹⁸ demonstrated a statistically significant increase in patients with a definite neurologic abnormality in the corticosteroid treatment group (RD = 10%; 95% CLs, 2% and 19%). Five studies^{24-26,29,30} showed no statistically significant difference in neurologic status at hospital discharge between treatment and control groups (range of RDs, -15% to 5%). For the seven studies with information available on neurologic outcome at hospital discharge, the combined RD was 0.2% (95% CLs, -11% and 12%, Fig 1). For the five pediatric studies, the combined RD was -9% (95% CLs,

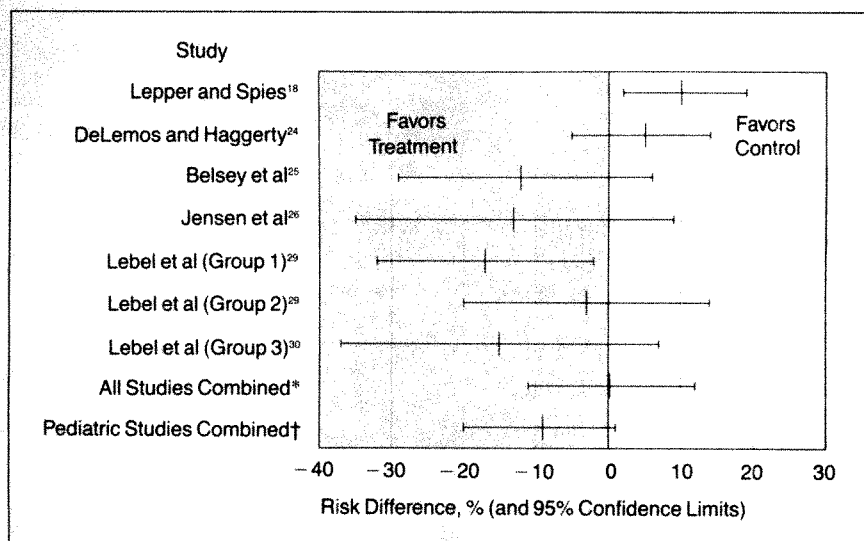


Fig 1.—Risk of neurologic abnormality at hospital discharge. Asterisk indicates weighted combination of the risk differences for all the studies³¹; dagger, weighted combination of the risk differences for data from the pediatric studies.^{24,25,29,30}

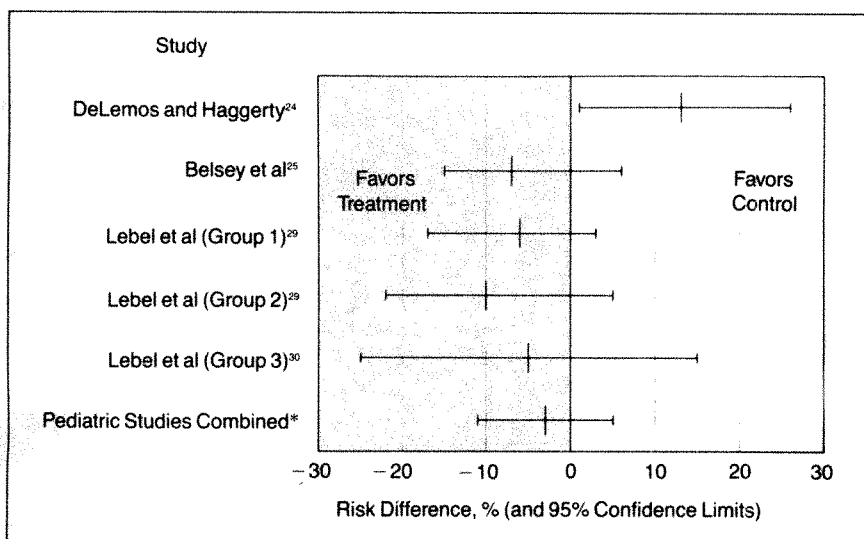


Fig 2.—Risk of neurologic abnormality at follow-up examination. Asterisk indicates weighted combination of the risk differences.³¹ The only studies reporting on neurologic status at follow-up examination were done with pediatric patients.

—20% and 1%.

Information concerning definite neurologic abnormalities at a follow-up examination at least 6 weeks after hospital discharge was available from five studies, all of which were carried out in pediatric patients (Fig 2). One study²⁴ showed a statistically significant detrimental effect of corticosteroid treatment (RD=13%; 95% CLs 1%, and 26%). Four trials^{25,29,30} showed no statistically significant difference between the treatment and control groups. When all studies were combined, the

overall RD was -3% (95% CLs, -11% and 5%).

Auditory function was assessed in only three trials (Table 2).^{29,30} Hearing tests were generally done within 6 weeks of hospital discharge, although the exact timing of the follow-up examinations cannot be determined from the published reports of two of the studies.²⁹ One trial showed a significant decrease in bilateral moderate or more severe hearing loss in the dexamethasone-treated group (RD = -16%; 95% CLs, -30% and -2%). The other two trials

showed an effect in the same direction that did not reach statistical significance.^{29,30} When these three trials are combined, the result favors steroid use, as the RD is -9% and the 95% CLs do not include 0 (-15% and -3%).

Complications of corticosteroid administration were not reported in most of the studies. There were three superinfections in the steroid group in one study.¹⁸ Gastrointestinal tract bleeding of sufficient severity to require blood transfusion developed in two patients who received corticosteroids.²⁹ One dexamethasone-treated patient had positive cerebrospinal fluid cultures after 10 days of antibiotic therapy.²⁹

COMMENT

Based on our analysis, there are insufficient data to support the routine use of corticosteroids as adjunctive therapy for patients with bacterial meningitis. The risk of moderate or more severe bilateral hearing loss is lower in patients treated with dexamethasone, based on pooled results from the three studies that assessed auditory acuity. However, combined results from nine available trials show no benefit of corticosteroid administration on risk of mortality, neurologic abnormality at hospital discharge, or neurologic abnormality at follow-up examination. These results do not change when separate analyses are done with data from studies performed only in children.

Meta-analysis can be a useful technique for combining results from multiple small studies with conflicting results.^{32,33} Optimally, studies included should be randomized, placebo-controlled, and double-blind. They should evaluate the same therapy in populations that are similar in age, disease, and disease severity. The same outcomes should be measured in similar fashion at similar follow-up times and should be reliably recorded.³³ The studies included in our meta-analysis do not meet all these criteria. The trials were carried out over 31 years, from 1958 through 1988. While they all employed concurrently treated control patients (by design), only six were placebo-controlled or double-blind. The corticosteroid type and dosage were different in all but three of the studies. The antibiotic type and dosage were different in all

Table 2.—Risk of Moderate or More Severe Bilateral Hearing Loss

Source, y	Risk, No. Affected/ Total in Group (%)		Risk Difference, % (95% Confidence Limits)*
	Treatment Group	Control Group	
Lebel et al (group 1), ²⁹ 1984-1985†	2/43 (5)	8/38 (21)	-16 (-31, -2)
Lebel et al (group 2), ²⁹ 1986-1987‡	1/49 (2)	5/46 (11)	-9 (-19, 1)
Lebel et al (group 3), ³⁰ 1987-1988§	1/30 (3)	2/29 (7)	-4 (-15, 8)
Total	4/122 (3)	15/113 (13)	-10 (-17, -3)
Combined risk difference¶	-9 (-15, -3)

*The risk in the treatment group minus the risk in the control group equals the risk difference. When the 95% confidence limits of the risk difference include 0, no statistically significant difference exists.

†Cefuroxime sodium, 240 mg/kg per day, was used for antibiotic therapy.

‡Ceftriaxone sodium was used for antibiotic therapy.

§Cefuroxime sodium, 300 mg/kg per day, was used for antibiotic therapy.

||The risk difference was calculated for each study separately using the method of Fleiss.³⁹

¶The risk difference was calculated for all the studies combined using the method of DerSimonian and Laird.³¹

of the studies. The populations studied differed in distribution of patient ages and causal agents. Outcome definitions were often not clearly stated, making it impossible to evaluate all the outcome variables of interest in many of the studies. The time to follow-up evaluation was extremely variable. Since neurologic abnormalities may resolve with time,⁴⁰ this could have a significant impact on the results of the trials we pooled.

To avoid some of the problems of combining data from studies carried out in different populations, we did separate analyses on data from five studies done primarily in children.^{24,25,29,30} *Haemophilus influenzae* type b was the cause of meningitis in 68% of cases in this group compared with 45% of cases overall and 15% of cases in the remaining four studies.^{18,21,26,28} There was no significant difference in the results when this subset was analyzed separately from all the other studies.

The results of this overview suggest that corticosteroid administration decreases the risk of hearing loss following bacterial meningitis. Three trials from a single institution assessed auditory acuity.^{26,30} All three employed dexamethasone as the therapeutic corticosteroid. One trial, using the antibiotic cefuroxime sodium at a dosage of 240 mg/kg per day for treatment of meningitis, showed

a significant reduction in hearing loss in the dexamethasone-treated group.²⁹ Another trial, using a higher dosage of cefuroxime sodium (300 mg/kg per day), showed no significant benefit from using corticosteroids.³⁰ The third study, using ceftriaxone sodium, also did not show a statistically significant benefit from dexamethasone.³⁰ The major difference in these studies is the incidence of moderate or more severe bilateral hearing loss in the placebo groups (Table 2), which varied from 21% in the lower-dosage cefuroxime trial²⁹ to 7% in the higher-dosage cefuroxime trial.³⁰ While the difference in these rates is not statistically significant ($\chi^2=2.6$, $P=.11$), a rate of moderate or more severe bilateral hearing loss of 21% is higher than the 6% to 15% incidence found in most recent studies of hearing loss following acute bacterial meningitis.^{13-15,41,42} This suggests that antibiotic choice and dosage may be important factors in the development of hearing impairment following bacterial meningitis.⁴³

Delayed sterilization of the cerebrospinal fluid may be a complication of corticosteroid use. In the one trial by Lebel and colleagues²⁹ that showed significant benefit from dexamethasone administration, cefuroxime was the antibiotic used to treat all patients. While cefuroxime penetrates well into

the cerebrospinal fluid when the meninges are inflamed, penetration becomes poorer as inflammation subsides.⁴⁴ Treatment with dexamethasone, which reduces meningeal inflammation, may result in decreased antimicrobial penetration into the cerebrospinal fluid, with failure to sterilize the cerebrospinal fluid. One patient in this trial²⁹ had a positive cerebrospinal fluid culture after 10 days of cefuroxime plus dexamethasone therapy. This relapse rate is similar to the 0.8% rate reported in a series of 708 patients with *Haemophilus meningitis* who did not receive corticosteroids.⁴⁵ However, persistently positive cerebrospinal fluid cultures have been reported in other patients treated with dexamethasone and penicillin for pneumococcal meningitis.⁴⁶ If corticosteroids improve hearing at the expense of adequate antimicrobial treatment of the underlying disease, the potential benefits do not outweigh the risks.

Other complications of corticosteroid use were poorly reported in most of the studies. Superinfection and gastrointestinal tract bleeding are possible,^{18,29} and it may be that patients treated with corticosteroids should also be treated with antacids, H₂ blockers (cimetidine or ranitidine), or sucralfate to protect against the possibility of serious gastrointestinal tract bleeding.

The findings of this meta-analysis do not support the routine use of corticosteroids in patients with bacterial meningitis. There is preliminary evidence that use of dexamethasone may decrease the incidence of hearing loss, but this is based on combined results of one positive and two negative studies done only in children. Seventy-seven percent of patients in those studies had meningitis caused by *H influenzae* type b. Generalization to meningitis caused by other organisms or to neonates and adults is not justifiable based on available data. If corticosteroids are used as adjunctive therapy to decrease the inflammation associated with bacterial meningitis, antibiotics with adequate cerebrospinal fluid penetration should be used to assure eradication of the infectious agent.

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Symmetrical Thalamic Degeneration With Calcifications of Infancy

Francis J. DiMario, Jr, MD, Robert Clancy, MD

• We describe the clinical and radiographic features of three premature infants with symmetric thalamic calcification recognized by computed tomographic scan on days 6, 12, and 49 of life and contrast our findings with those reported in the literature. These lesions follow prepartum or intrapartum hypoxia-ischemia and are clinically distinguished by prominent bulbar dysfunction, featuring weak or absent cry, poor feeding, and facial weakness. Neonatal thalamic calcification in premature infants may serve as a radiological marker of an acute, short-lived hypoxic-ischemic event. The presence of brain-stem dysfunction, particularly of lower cranial nerves in association with thalamic calcifications, constitutes a distinctive clinical-radiological entity and usually portends a poor outcome. The presence of these calcifications implies that injury was sustained to diencephalic and brain-stem structures at least 2 to 4 weeks prior to their appearance on computed tomographic scan.

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There are several patterns of brain injury that may follow hypoxia-ischemia in the human newborn. Different pathophysiologic mechanisms have been proposed to explain the spatial topography of neuropathologic disease and its corresponding clinical correlates.

The rather distinctive clinical and pathological features of hypoxic-ischemic injury maximally involving the diencephalon and brain stem have been infrequently reported.^{1,2} The radiological correlates of this pattern of central nervous

system damage are even less well characterized, and premorbid identification of these calcifications by neuroimaging has been rare.^{4,7,9-11} Neuronal loss and calcification have been identified at autopsy within the thalamus and brain stem in only a few previously reported cases.^{1,8} Similar lesions have been reported only once within the first week of life.⁶ We describe three new cases of this rare but dramatic entity and contrast our patients with those described in the literature. We emphasize the occasional presence of prepartum-onset hypoxia-ischemia, the need for early computed tomographic (CT) imaging, the prominent and persistent clinical signs of bulbar dysfunction, and the uniformly poor neurologic prognosis.

PATIENT REPORTS

PATIENT 1.—A female infant was born via spontaneous vaginal delivery at 35 weeks' gestation after a pregnancy complicated by polyhydramnios. Apgar scores were 8 at 1 minute and 8 at 5 minutes. She required no delivery room resuscitation. The birth weight was 2450 g (45th percentile) and her head circumference was 33 cm (60th percentile). There were no dysmorphic features. From the time of birth she displayed little spontaneous activity and was not visually attentive. Brain-stem abnormalities were prominent. Eye movements were full and intermittent ocular bobbing was noted. She had symmetric but reduced spontaneous facial movements. There was a weak cry, minimal tongue movements with no fasciculations, and absent gag, suck, and swallow. She was mildly hypotonic and maintained a frog-legged posture. Deep tendon reflexes were brisk with several beats of ankle clonus bilaterally. No seizures or involuntary movements were observed. At 6 days of age, an electroencephalogram (EEG) was normal and a CT scan of the head revealed bilateral thalamic calcifications and a small right frontal subdural hematoma (Figure, top). Examination at 8 weeks of age revealed a more vigilant infant with improved spontaneous movement. There was no visual fixation. Extraocular movements were full with a diver-

gent gaze in primary position. The infant continually drooled. Absent gag, suck, and swallow persisted, necessitating nasogastric gavage feedings. She gradually assumed an arched truncal posture with increased extensor tone of all extremities and subsequently developed seizures requiring long-term anticonvulsant therapy. She remains severely impaired neurologically at 30 months of age with spastic quadriplegia, failure to thrive, and marked global delay with motor and mental development below a 3-month level.

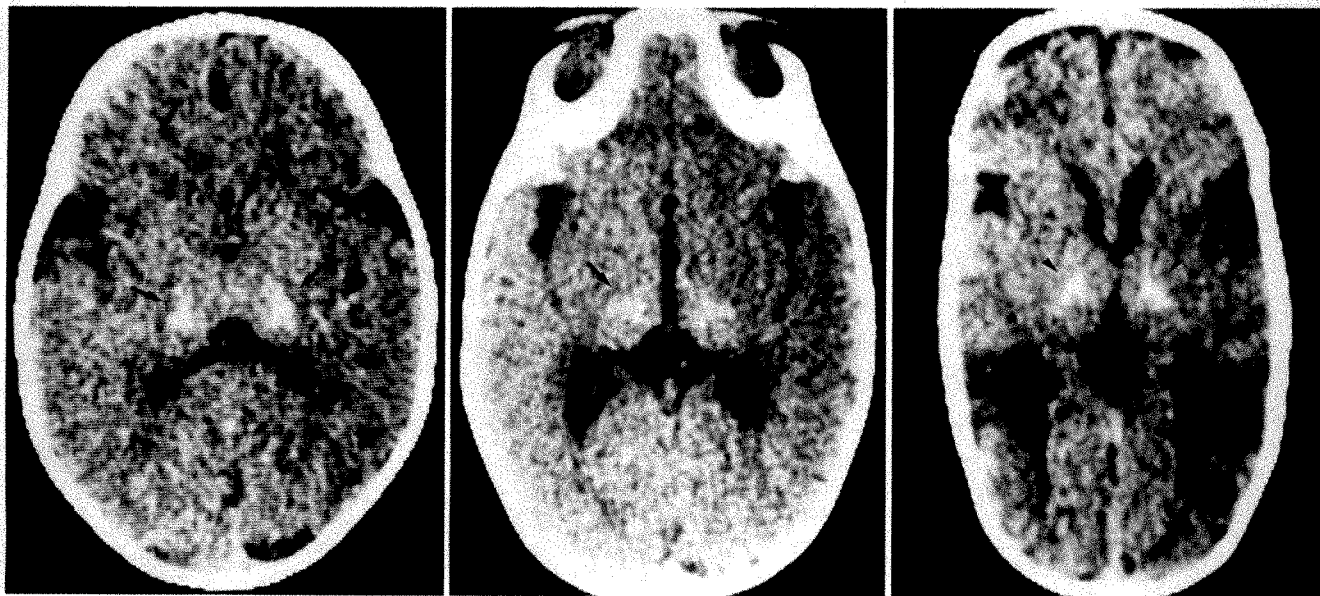
PATIENT 2.—A female infant, the 2280-g (60th percentile) product of an uncomplicated 33-week gestation, was born via vaginal delivery in breech presentation. Apgar scores were 2 at 1 minute and 5 at 5 minutes. She was severely depressed at birth, requiring immediate intubation and resuscitation in the delivery room but was extubated within several hours. She required intravenous anticonvulsant therapy with phenobarbital sodium, phenytoin sodium, and paraldehyde for status epilepticus noted at 8 hours of life. Examination revealed a normocephalic (head circumference 31 cm; 50th percentile) nondysmorphic infant who had little spontaneous movement. She was not alert and would not visually fixate. She had a very poor suck, no gag, and was diffusely hypotonic with an absent Moro's reflex. An EEG obtained at 2 days of age was extremely low voltage, evolved into a burst-suppression pattern by 4 days of life, and displayed multifocal spikes and sharp-waves with diffuse slowing by day 12 of life. A head CT scan then suggested brain-stem atrophy and revealed diffuse calcification in the thalami and brain stem (Figure, center). She required nasogastric gavage feedings and ultimately a gastrostomy tube for nutrition. Subsequent ophthalmologic examination at 3 weeks of age revealed optic atrophy bilaterally. At age 6 months, she developed infantile spasms and a hypsarrhythmic EEG. At a 40-month follow-up visit, she had microcephaly, severe spastic quadriplegia, and profound psychomotor retardation.

PATIENT 3.—A female infant was born after 33 weeks' gestation. The pregnancy was complicated by first-trimester maternal treatment of ulcerative colitis with sulfasalazine and the identification by fetal ultrasound examination of a neck mass that suggested

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Patient 1 (left) and patient 2 (center). Noncontrast computed tomographic scan of the head, axial view. Note bilateral thalamic calcifications (arrows). Patient 3 (right). Noncontrast computed tomographic scan of the head, axial view. Note bilateral thalamic calcifications (arrowheads) and hypodense parieto-occipital cortices.

the presence of a cystic hygroma. An amniocentesis was performed during the second trimester that revealed a normal karyotype. Follow-up serial fetal ultrasound examinations demonstrated complete resolution of the neck mass. The infant was born via cesarean section due to breech presentation. Apgar scores were 1 at 1 minute and 6 at 5 minutes. The infant was briefly intubated in the delivery room but extubated prior to transfer to the nursery. Initial physical examination showed a birth weight of 1300 g (third percentile) and head circumference of 27 cm (less than third percentile). She had a flat nasal bridge, micrognathia, mildly redundant nuchal skin, and a high arched palate. She did not cry or suck and was hypotonic. She developed episodes of apnea and mild respiratory distress requiring reintubation by 6 hours of life. Subsequent evaluation included a normal head ultrasound examination, a normal chest roentgenogram, and negative elevations in antibody titers to toxoplasmosis, rubella, cytomegalovirus, or herpes virus. The infant continued to require mechanical ventilation secondary to recurrent apneic episodes and was transferred to our facility for further evaluation at 7 weeks of age.

Physical examination then revealed a weight of 2.3 kg and head circumference of 31.2 cm. She was mildly dysmorphic as detailed above. Her head shape was dolichocephalic, and she remained in an opisthotonic posture with retrocollis. She was alert, with spontaneous eye opening and visual fixation. There was a paucity of spontaneous body

movement with no behavioral manifestations of crying following noxious stimulation. Extraocular movements, fundi, and pupillary light reactions were normal. She manifested a facial diparesis, worse on the left side. There was no suck, gag, or palatal movement. Bilateral vocal cord paralysis was noted by direct laryngoscopy. The tongue displayed hemiatrophy of the left side and abundant fasciculations. She was hypertonic with diffusely brisk deep tendon reflexes. She withdrew from a pinprick to all four extremities. A head CT scan revealed bilateral thalamic calcifications, hypodensities in the parieto-occipital junctions bilaterally, and prominence of the cerebrospinal fluid spaces in the posterior fossa (Figure, bottom). An EEG was mildly abnormal due to increased background discontinuity and excessive temporal sharp transients. She subsequently required a tracheostomy to receive continuous positive-pressure mechanical ventilations and a nasogastric gavage tube for feeding.

COMMENT

There are four principal brain lesions that may occur in premature infants: matrix-zone hemorrhage, periventricular leukomalacia, white-matter gliosis, and necrosis of the thalamus with or without involvement of the basal ganglia and brain stem.^{12,13} The characteristics of brain injury seen in full-term infants include diffuse corticoneuronal injury, parasagittal "watershed" infarctions, and subcortical leukomalacia. The

pathogenesis of these specific varieties of brain injury reflects different patterns of impaired cerebral perfusion with relative involvement or sparing of specific brain regions.¹² This regional disease has characteristic clinical correlates in both the neonatal period and later life.

A review of the literature¹⁴ reveals only eight previous studies concerning 12 infants who had clinical neurologic evidence of brain-stem injury and pathological evidence of mineralization of the thalami (Table). Computed tomographic scan results were available in only four of these, with abnormal findings in two.

Thalamic and brain-stem injury manifest as prominent bulbar dysfunction out of proportion to the patient's impairment of consciousness. Most often recognized are disordered sucking and swallowing, crying, glossoparesis, and oculomotor difficulties. Although mental status may be depressed initially, the abnormal bulbar signs persist despite the return of normal vigilance. Late sequelae include spastic quadriplegia, hypotonia, movement disorders, mental retardation, and seizures. Similar observations were made in our patients. Despite mild requirements for resuscitation at birth, each displayed profound brain-stem dysfunction. Ab-

Summary of Clinicopathological Cases of Infantile Thalamic Calcifications*

Source, y	Patient	Prenatal Birth History	Gestational Age	Apgar Scores, 1 min/5 min	Clinical Examination, Course	Neuroimage	Pathologic Findings
Rosales and Riggs, ¹ 1962	1	Polyhydramnios	Term	NS	Apneic at birth, required intubation; hypotonic with hyperreflexia; no suck or swallow; NG fed; died at 6 mo	ND	Lateral thalamic atrophy with astrocytic glial hyperplasia and "fossilized" neurons
	2	Polyhydramnios	Term	NS	Cried but flaccid tone and no spontaneous movement at birth; developed opisthotonos, seizures, and apnea; no suck or swallow; NG fed; died at 15 mo	ND	Lateral thalamic atrophy with astrocytic glial hyperplasia and "fossilized" neurons
	3	Uncomplicated	Term	NS	Birth history NS; no suck or swallow; NG fed; died at 16 mo	ND	Lateral thalamic atrophy with astrocytic glial hyperplasia and "fossilized" neurons
Norman, ² 1972	1	NS	Term	1/NS	Intubated at birth; NG fed; at 1 mo: poor suck, eyes turned downward; opisthotonic, spastic; developed seizures and died of aspiration pneumonia at 6 wk	ND	Patchy neuronal loss with encrusted neurons and hypertrophied astrocytes in the thalamus and reticular formation of medulla and pons
	2	Maternal salicylate overdose; breech	34 wk	1/NS	Stridor at birth, intubated; comatose with eyes deviated to right; no suck, grasp or Moro's reflex; flaccid and areflexic with ankle clonus; died at 1 wk	ND	Extensive neuronal loss, encrustation of neurons, and hypertrophied astrocytes in thalamus and bilateral reticular formation from rostral medulla to midbrain
	3	Polyhydramnios	34 wk, low forceps	2/NS	Flaccid, stridorous; intubated, fixed and dilated pupils, with clonus of the left leg; died at 8 d	ND	Neuronal loss, encrusted neurons, and pronounced increase of glia bilaterally of reticular formation, entire brain stem, and thalamus
Ambler and O'Neil, ³ 1975	1	Uncomplicated	42 wk	NS	Apneic at birth; developed opisthotonos and hypertonia by 2 h of age; no suck; NG fed; episodic apnea and bradycardia; died at 3 wk	ND	Severe thalamic cell loss and astrogliosis with cytoplasmic calcoppherules
Abuelo et al., ⁴ 1981	1	(Same case as Ambler and O'Neil; see above)					
	2	Uncomplicated	Term	2/8	Rigid with flexed arms and scissoring legs; apnea at 10 d with development of seizures; died at 2 mo	CT scan of head at 10 d and skull roentgenogram were normal	Microgyria with major neuronal loss and gliosis in thalamus and white matter; mineral concretions in the thalamus
Wilson et al., ⁵ 1982	1	Uncomplicated until loss of variability on fetal monitoring; thick meconium	36 wk	6/6	Intubated at birth; pinpoint pupils; no spontaneous eye movements, gag, suck, or grimace; areflexic and flaccid; seizures at 8 h; died at 16 d	CT scan of head at 4 d was normal	Prominent neuronal loss with mineralization and gliosis of thalamus and multiple cranial nerve nuclei

(cont)

sent gag, absent suck, and weak cry in concert with oculomotor abnormalities and hypotonia summarize their characteristic findings. One patient also developed status epilepticus within the first several hours of life, which suggests a

more global hypoxic-ischemic event involving the cortex. Long-term follow-up is available in two of these patients. Each suffers from severe residual neurologic impairment.

The clinical history and time of detec-

tion of thalamic and brain-stem calcification by CT scan may help date the onset of injury. Wilson et al⁵ described an infant with evidence of intrapartum asphyxia whose CT scan at 4 days of life was normal but whose autopsy at 16

Summary of Clinicopathological Cases of Infantile Thalamic Calcifications* (cont)

Source, y	Patient	Prenatal Birth History	Gestational Age	Apgar Scores, 1 min/5 min	Clinical Examination, Course	Neuroimage	Pathologic Findings
	2	Insulin-dependent diabetes mellitus	36 wk	5/NS	Hypotonic with weak cry and facial diplegia; no suck, gag, palatal, or tongue movement, with tongue fasciculations; treated for hypoglycemia; died at 12 d	ND	Necrosis of mesencephalon and reticular formation, with most prominent lesions in thalamus associated with calcifications
	3	Uncomplicated; CS	32 wk	"moribund"	Intubated immediately; died at 3 h	ND	Periventricular leukomalacia with mineralization, neuronal loss, astrocytosis, and gliosis of reticular formation, thalamus, and elsewhere
Parisi et al, ⁶ 1985	1	Arrested premature labor at 32 wk; CS for double-footling breech	36 weeks	4/7	Apneic, hypertonic flexor posture; poor suck and swallow; NG fed; episodic apnea; died at 4 wk	CT scan of head showed bilateral thalamic densities	Symmetrical patchy areas of severe neuronal loss, astrocytosis, and mineralized neurons within the thalamus; gliosis of brain-stem tegmentum
Roland et al, ⁷ 1988	1	Variable decelerations 1 h prior to birth; sustained bradycardia for 15 min prior to midforceps delivery	Term	1/1	Pale, flaccid, and apneic at birth; required intubation and resuscitation; seizures at 1 h; remained comatose with absent oculocephalic responses; no gag or suck; marked facial diplegia, bilateral ptosis, retrognathia, and tongue fasciculations; required gastrostomy; died at 4 mo	CT scan of head at 5 d was normal; CT scan of head at 14 d showed decreased attenuation, basal ganglia; CT scan of head at 30 d showed dilatation of third ventricle, increased attenuation of tissue adjacent to third ventricle, and tissue loss in thalamus/basal ganglia	Extensive neuronal loss and gliosis of thalamus and brain stem; no hypervascularity in thalamus; dead encrusted neurons adjacent to fourth ventricle and throughout both brain stem and thalamus
Present series	1	Polyhydramnios	34 wk	8/8	At birth, hypotonic with decreased spontaneous activity; poor suck and swallow; NG fed; developed opisthotonos and hypertonicity with cortical blindness, recurrent seizures, and severe developmental delay	CT scan of head at 5 d showed bilateral thalamic calcifications	ND
	2	Uncomplicated breech delivery	36 wk	2/5	Apneic and hypotonic at birth; required intubation and resuscitation at birth; developed seizures at 8 h; required NG feedings for continued poor suck and swallow; at 40 mo had microcephaly, quadriplegia, chronic seizure disorder, and severe developmental delay	CT scan of head at 12 d showed calcification of bilateral thalami and upper brain stem	ND
	3	Maternal treatment with sulfasalazine early first trimester; in utero cystic hygroma resolved; CS for breech	33 wk	1/6	Apneic and hypotonic at birth with little spontaneous activity; no suck or swallow; NG fed; developed hypertonicity, tongue atrophy with fasciculations; and facial diplegia; required tracheostomy	CT scan of head at 49 d showed bilateral thalamic calcifications and ischemic changes of parieto-occipital cortices	ND

*NS indicates not stated specifically; NG, nasogastric gavage; ND, not done; CT, computed tomographic; and CS, cesarean section.

days demonstrated mineralization of diencephalic and brain-stem structure. Abuelo et al⁴ described an infant with a normal 5-minute Apgar score with rigidity and scissoring of the legs noted immediately at birth. The CT scan at day 10 of life was normal, but significant neuronal loss with mineral deposition was present in the thalamus at autopsy 2 months later. Roland et al⁷ described an asphyxiated infant born following significant intrapartum distress who was studied serially by head CT scan examinations. On the fifth postnatal day the CT scan was normal, but by the 14th postnatal day there was decreased attenuation of the basal ganglia. On day 30 of life there was increased attenuation noted in these areas on CT scan as well as tissue loss in the thalamus and basal ganglia. Autopsy at 4 months demonstrated gliosis and encrusted neurons in this region without concomitant hypervascularity. These findings prompted the authors to propose that the increased density seen on CT scan likely reflected reactive gliosis rather than capillary proliferation as has been previously suggested.⁹ Their observations suggest that the development of increased attenuation or calcification of the brain stem and diencephalon to a degree that can be identified by CT may take as long as 2 to 4 weeks after the initial insult.

The neuropathologic examination of prenatally acquired brain injury demonstrates many possible abnormalities: astrocytic hypertrophy, microglia and macrophage infiltration, capillary proliferation, ferrugination, and cystic changes.^{13,14} Ferrugination describes the process by which necrotic cells become encrusted by mineral deposits. The intracellular deposit of iron and calcium salts occurs relatively late after cell death. At least 14 days are required before this response will be observed.¹⁴ The observation of brain mineralization demonstrated by CT or by neuropathologic examination are in good agreement and date the lesion as at least 2 weeks old.

In light of these previous studies and ours, we propose that two clinical patterns emerge in infants with thalamic calcification. The first includes those who suffered *prenatal* injury, as evidenced by polyhydramnios, breech presentation, absence of overt labor com-

plications, spasticity at birth, tongue fasciculations, and the very early identification of thalamic calcifications on CT scan. These infants constitute the majority of patients. Their prenatal injury results in profound bulbar impairment, which renders the infant vulnerable for an "acute asphyxia" at birth. This occurs by virtue of an impaired respiratory drive, diminished capacity to protect the airway, and obstructive apnea secondary to weak pharyngeal musculature. Collectively, these may cause low Apgar scores. In the immediate postdelivery period, the classic signs of acute hypoxic-ischemic encephalopathy may then be superimposed producing hypotonia, seizures, pupillary disturbances, and EEG abnormalities. Infants who do not sustain secondary perinatal asphyxia at birth are more likely to demonstrate clinical findings suggestive of a chronic central nervous system injury such as hypertonicity, rigidity, opisthotonos, athetoid movements, or hyperactive gag reflex.¹² Abuelo et al⁴ and Parisi et al⁶ described infants who typify this pattern of symmetrical thalamic calcification. They exhibited spasticity at birth in combination with bulbar dysfunction and had severe bilateral thalamic neuronal loss with mineralization at autopsy. A CT scan revealed thalamic hyperdensities at 5 days of age.⁶ The clinical findings at birth of hypertonicity, contractures, micrognathia, and/or a high-arched palate in combination with significant brain-stem dysfunction suggest in utero injury. The presence of calcifications on CT scan performed near the time of birth confirms the prenatal onset of the lesions.

The second and less common pattern of presentation includes those patients who had an uncomplicated prenatal course but who sustained significant intrapartum difficulties. These infants have had no history of polyhydramnios and do not immediately manifest tongue fasciculations or other findings suggestive of chronic central nervous system injury. They experience late fetal distress and appear acutely asphyxiated at birth. These infants progress through an evolving sequence of clinical manifestations usually seen in severe acute asphyxia. However, as their mental status and activity improve, signs of bulbar dysfunction persist and dominate the clinical picture at first. Early CT scans

do not reveal the thalamic calcifications, although studies performed later do. Our patient 2 conforms to this group of patients. Similarly, Wilson et al⁵ describe a patient who suffered well-documented fetal and intrapartum distress. This infant appeared acutely asphyxiated at birth and had a normal CT scan within the first week of life. However, by 16 days of age, autopsy revealed thalamic mineralization.

Thus, the timing of the CT identification of thalamic calcification taken in context with the physical examination at birth and the clinical evolution thereafter can help determine whether injury was likely to have been sustained prenatally or during the immediate intrapartum period.

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Klebsiella pneumoniae Bacteremia in Children

Fifty-Seven Cases in 10 Years

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• A review was performed of the 57 cases of *Klebsiella pneumoniae* bacteremia that occurred in children at our institution during a 10-year period. The rate of *K pneumoniae* bacteremia relative to all blood cultures in which bacteria were isolated was 1.1%. Children younger than 12 months of age accounted for 38 cases (67%). There were 8 children (14%) who were afebrile at the time bacteremia was documented; other presenting clinical features were generally indistinguishable from those that characterize pediatric bacteremia of more common causes. Fourteen children (25%) were receiving broad-spectrum parenteral antibiotic therapy at the time bacteremia was documented. In 53 patients (93%), an underlying condition predisposing to opportunistic infection was identified, the most common of which were lesions of the gastrointestinal tract (56%), presence of an indwelling central venous catheter (35%), and neutropenia (25%). *Klebsiella pneumoniae* was a constituent of polymicrobial bacteremia in 15 patients (26%). The overall mortality rate associated with this infection was 20%, with over one half of all deaths occurring in infants who were afebrile at the time bacteremia was documented. *Klebsiella pneumoniae* bacteremia is a relatively uncommon, serious infection that usually occurs in young children with predisposing underlying conditions, and is associated with a significant mortality rate.

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Klebsiella pneumoniae bacteremia is a relatively rare infectious disorder in children. I know of no previous survey that has been performed to characterize cases of pediatric *K pneumoniae* bacteremia.

This study reviewed all cases of pediatric *K pneumoniae* bacteremia that occurred at our institution during a 10-year period to delineate the clinical features characterizing this infectious disorder.

PATIENTS AND METHODS

A review was performed of the medical records of all patients for whom the results of a blood culture were positive for *K pneumoniae* at the Children's Hospital of Wisconsin, Milwaukee, from 1979 to 1988. Nosocomial infection was one that occurred after 3 days of hospitalization.¹ Antibiotic therapy was considered adequate if there was administration of one or more antimicrobial agents with in vitro activity against the corresponding isolate. Deaths were considered to be contributed to by sepsis if they occurred while patients received treatment for bacteremia, unless clear clinical and pathologic data suggested otherwise.

RESULTS

During the study period, bacteria were isolated in a total of 5156 blood cultures; *K pneumoniae* accounted for 60 isolates. In 57 of the 60 cases, the clinical course was consistent with sepsis. Three other cases were considered to be contaminants. In each of these cases, a previously healthy child was discharged after outpatient evaluation for a febrile illness without receiving antibiotic therapy, and no patients required reevaluation within the subsequent 72-hour period.

Of the 57 patients with *K pneumoniae* bacteremia, the range of ages was 2 days to 19 years: 9 patients were younger than 2 months of age, 29 patients were aged 2 to 12 months, 5 patients were aged 12 to 24 months, 6 patients were aged 2 to 5 years, and 8 patients were older than 5 years of age. There were 34 boys and 23 girls. The racial

distribution included 35 whites, 19 blacks, and 3 Hispanics. Bacteremia was classified as a nosocomially acquired infection in 43 patients (16 patients were receiving care in an intensive care unit). At the time bacteremia was documented, 8 patients were afebrile and 2 patients were hypotensive (requiring pressors).

In general, other presenting clinical features associated with *K pneumoniae* bacteremia were similar to those that characterize the more common causes of pediatric bacteremia. Of note was an otherwise healthy patient with asthma and acute bronchospasm who developed fever and roentgenographic evidence of bilateral perihilar pulmonary infiltrates after receiving parenteral corticosteroid medication for 7 days, and had 3 sequential blood cultures performed during a 72-hour period with positive results for *K pneumoniae*.

Broad-spectrum combination parenteral antibiotic therapy was administered at the time nosocomial bacteremia was documented in 14 cases; in 12 of these cases, antibiotic therapy was adequate, and in 2 cases, the isolate was resistant to the regimen used. During the course of their illnesses, 8 patients (all with nosocomial infection) who were receiving adequate antibiotic therapy that included an aminoglycoside to which the organism was susceptible had at least one blood culture obtained subsequent to the initial positive culture with results that were also positive for *K pneumoniae*. In 7 of these cases, patients were receiving chemotherapy for malignancy or were neutropenic. In 15 patients, *K pneumoniae* was a constituent of polymicrobial bacteremia; 8 of these patients had an underlying lesion of the gastrointestinal tract.

In the 57 cases, a total of 112 clinical

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Underlying Conditions Associated With <i>Klebsiella pneumoniae</i> Bacteremia	
Underlying Condition	No. of Patients
Gastrointestinal tract	
Short-gut syndrome	8
Failure to thrive	6
Cholangitis	5
Bowel obstruction	3
Intra-abdominal abscess	3
Peritonitis	3
Hepatic failure	1
Fistula	1
Necrotizing enterocolitis	1
Perirectal abscess	1
Indwelling central venous catheter	20
Neutropenia*	14
Respiratory tract	
Pneumonia	8
Mechanical ventilation	4
Asthma/corticosteroid therapy	1
Malignancy/chemotherapy	
Acute lymphocytic leukemia	7
Lymphoma	3
Hepatoblastoma	1
Urinary tract	
Infection	4
Obstruction	4
Nephrotic syndrome	1
Neonate/prematurity	5
Congenital heart disease	4
None identified	4

*Absolute neutrophil count less than $1 \times 10^9/L$.

entities were identified that were considered predisposing factors to opportunistic infection (Table). Of the 11 patients who died, all had nosocomial bacteremia, 5 had polymicrobial bacteremia (*K pneumoniae* combined with *Citrobacter diversus*, *Escherichia coli* and *Enterobacter cloacae*, *E. cloacae*, enterococcus and *Staphylococcus epidermidis*, *Pseudomonas aeruginosa* and *E. coli*, and *Staphylococcus aureus*), and 6 (all younger than 12 months of age) were afebrile at the time bacteremia was documented. Autopsy was performed in 3 patients, none of which revealed findings consistent with a specific cause of death other than sepsis.

COMMENT

Klebsiella pneumoniae is a gram-negative encapsulated bacillus of the family Enterobacteriaceae, found to colonize the gastrointestinal and respiratory tracts of hospitalized patients.² Invasive infection is usually nosocomially acquired by the compromised host. This organism is one of the most common causes of nosocomial bacteremia in

children,³ and following *E. coli* is the second leading cause of all nosocomial gram-negative infections in both children³ and adults.^{4,6}

I know of no previous survey that has characterized pediatric cases of *K pneumoniae* bacteremia. In this series, the majority of instances of this infection occurred in younger children, with two thirds of the patients younger than 12 months of age. Bacteremia due to this organism was a nosocomially acquired infection in 75% of the cases, similar to the 77%⁴ and 84%⁵ rates of nosocomially acquired *K pneumoniae* bacteremia in adults. Approximately 25% of the children were receiving broad-spectrum antibiotic therapy at the time bacteremia was documented, reinforcing the concept that antimicrobials may exert selective pressure on normal flora that favors colonization with this organism in hospitalized patients.⁷

The overall mortality rate of 20% observed in this series is similar to the 25%⁴ and 16%⁵ mortality rates documented in adults with *K pneumoniae* sepsis. Specifically, we found that afebrile children younger than 12 months of age represented over one half of all deaths. Perhaps the inability to mount a fever by the compromised, young child with systemic infection is an index of inadequate host response and poor prognosis.

Many of the characteristics of children with *K pneumoniae* bacteremia were uniquely different from those described in adult cases. The overall isolation rate of this organism by blood culture was only 1.1% relative to all blood cultures in which bacteria were isolated, less than the 6.6% rate documented in adults.⁴ In 14% of the cases, the patients were afebrile at the time bacteremia was documented. Although this is three times the rate of afebrile adults with *K pneumoniae* bacteremia previously described,⁴ it is consistent with the rate of afebrile children with more common causes of pediatric bacteremia.⁸ Compared with the 22% rate of associated shock described in an adult series,⁴ only 3.5% of the children experienced this complication. This lower rate may, in part, reflect the level of ongoing, in-hospital monitoring taking place for many children known to have serious underlying conditions when bacteremia

developed, prompting early and aggressive treatment.

Almost all instances of *K pneumoniae* bacteremia were associated with at least one underlying condition considered to be a predisposing factor for opportunistic infection. In contrast to adult series in which the urinary, respiratory, and gastrointestinal tracts were the three most common sources of *K pneumoniae* bacteremia,^{4,5} we found that lesions of the gastrointestinal tract (56%), the presence of an indwelling central venous catheter (35%), and neutropenia (25%) were the predominating conditions in children; an underlying lesion of the urinary tract was identified in only 16% of the pediatric cases.

The association of the presence of indwelling central venous catheters with *K pneumoniae* bacteremia has been demonstrated in the adult literature.^{9,10} There was a noted propensity for persistent bacteremia in those patients with underlying immunodeficiency states (neutropenia and chemotherapy administered for malignancy), despite receiving adequate antibiotic therapy. Also of note was an otherwise healthy child with asthma who developed nosocomial pneumonia and persistent *K pneumoniae* bacteremia while receiving corticosteroid medication. Administration of corticosteroids can be a predisposing factor for the development of gram-negative sepsis in certain hosts¹¹; one should be aware of this potential complication, even in otherwise healthy children with asthma when corticosteroid therapy is used.

Klebsiella pneumoniae was a constituent of polymicrobial bacteremia in 26% of the cases, higher than the 12%⁴ and 16%⁵ rates of a polymicrobial cause observed in adult series of gram-negative bacteremia. The most common predisposing factor associated with polymicrobial bacteremia was an underlying lesion of the gastrointestinal tract, a finding similar to that noted in a previous report of pediatric polymicrobial bacteremia of diverse causes.¹² Polymicrobial bacteremia in which *K pneumoniae* was a constituent denoted a poor prognosis, with death occurring in one third of the cases. Yet, this mortality rate does not differ from that previously described in children with polymicrobial bacteremia of diverse causes.^{12,13}

Klebsiella pneumoniae bacteremia is a relatively uncommon but serious pediatric infection that usually occurs in younger children with predisposing underlying conditions. A significant mor-

tality rate is associated with *K pneumoniae* bacteremia, especially in those patients who are afebrile or experience polymicrobial bacteremia. When *K pneumoniae* bacteremia occurs, a thor-

ough investigation should be performed to identify a possible underlying condition predisposing to this opportunistic infection.

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In Other AMA Journals

ARCHIVES OF SURGERY

Congenital Idiopathic Corneal Endotheliopathy

Douglas R. Scott, MD; Jay S. Pepose, MD, PhD; Steven F. Lee, MD; Norman C. Charles, MD; Robert C. Cykiert, MD; Joaquin Barraquer, MD; Zennida de la Cruz; W. Richard Green, MD (*Arch Surg.* 1989;124:1186-1192)

Fiberoptic Bronchoscopy in the Treatment of Intubated Neonates

Eric S. Shinwell, LRCP, MRCS; Rosemary D. Higgins, MD; Richard L. Auten, MD; Donald L. Shapiro, MD

• A study of the role of fiberoptic bronchoscopy in intubated neonates was conducted. The study aimed to ascertain the applicability of fiberoptic bronchoscopy for assessment of endotracheal tube tip position, and to assess the incidence and clinical significance of airway disease in unselected patients. Seventy examinations on 65 neonates were performed without interruption of mechanical ventilation. The procedure was well tolerated in all cases. The accuracy of bronchoscopic measurement of endotracheal tube tip position improved markedly with user experience and reached a correlation of .96 with a chest roentgenogram. Although the technique was safe and accurate, the need for available and skilled personnel may limit the applicability of this method for endotracheal tube tip position assessment. Significant airway disease requiring a change in treatment was found in 13 patients (19%). This high incidence of significant but clinically unsuspected airway disease suggests that there should be more frequent consideration of diagnostic bronchoscopy in all sick intubated neonates who are at risk for airway disease.

(AJDC. 1989;143:1064-1065)

The development of ultrathin fiberoptic bronchoscopes has made routine bronchoscopic examination of the neonatal airway a practical possibility. Although the available instruments are limited by a lack of distal angulation and by reduced image resolution, they offer the potential for routine bedside examination of sick intubated neonates.

Vigneswaran and Whitfield¹ studied the use of a 1.8-mm fiberoptic bronchoscope (Olympus, Columbia, Md) for confirmation of endotracheal tube

(ETT) position in 20 intubated infants. They reported that the procedure was accurate and safe, noting only a small drop in transcutaneous PO_2 associated with both bronchoscopy and chest roentgenography. Airway disease was not reported in these neonates. Wood and Postma² and Wood³ described an extensive experience with bronchoscopic examination of neonates for specific indications, such as airway stenosis, plugging or compression, stridor, atelectasis, and difficult intubation. The ultrathin bronchoscope was found to have limited application because of the lack of distal angulation and occasional difficulty in identifying the carina with certainty. This problem was partially overcome in this study by alteration of head position combined with swiveling of the bronchoscope about its long axis; the slight angulation present in the bronchoscope facilitated directions into each of the major bronchi. Fan et al⁴ have described extensive experience with a 2.7-mm bronchoscope (Olympus), mostly in older infants. This instrument has the advantage of a directable tip but is limited by the absence of a suction channel. In addition, it will not pass an ETT smaller than 3.5 mm.

Thus, this study was conducted to assess the safety, accuracy, and applicability of fiberoptic bronchoscopy for routine determination of ETT position and for assessment of airway disease in an unselected group of sick intubated neonates.

METHODS

This study was approved by the Human Investigation Committee of the University of Rochester (NY) Medical Center. Neonates studied had been intubated or reintubated within the preceding hour, and each underwent both chest roentgenography and fiberoptic bronchoscopy. Neonates were selected at random for study when a bronchos-

copist was available. The ETT-carina distance on the roentgenogram was independently read by the neonatologist or neonatology fellow on call.

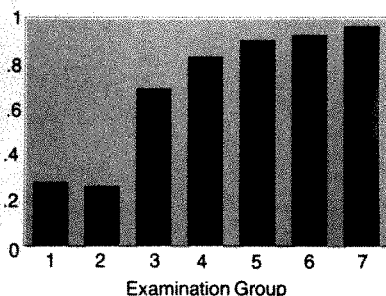
Bronchoscopy was performed by one of three individuals (E.S.S., R.D.H., or R.L.A.). The bronchoscopes (Visicath, Microvasive, Milford, Mass) employed were either 1.3 or 2.0 mm in external diameter, depending on the size of the neonate. The 2-mm bronchoscope has 0.4- and 0.9-mm channels: the 0.4-mm channel was used for oxygen, lavage, or clearing the viewing screen, and the 0.9-mm channel was used for suctioning, usually requiring relatively high negative pressure. The bronchoscope was introduced into the ETT via an elbow connector (Baxter-Airlife, McGaw Park, Ill), which was specially adapted with a small hole to accommodate the bronchoscope and thus allow for uninterrupted mechanical ventilation. The bronchoscope was advanced to the carina; the bronchoscopist placed a finger at the entry of the scope into the ventilator system and pulled back until the ETT tip came into view. The distance was measured and recorded. If the ETT was in the right main bronchus, this was diagnosed by the nature of bifurcation seen, and the ETT was then pulled back under direct vision until the carina was seen. The procedure was always performed with the head positioned as for the chest roentgenogram. A survey of the trachea and major bronchi to the lower lobe bifurcations was performed, and abnormalities were noted. As the bronchoscopes have no distal angulation, entry into the major bronchi was obtained by manipulation of the infant's head and swiveling the bronchoscope about its long axis. This was usually accomplished without difficulty, although this skill did appear to improve with investigator experience. During the procedure, the infant's condition was followed with pulse oximetry or transcutaneous oxygen monitoring. No changes were made in the infant's ventilator settings or oxygen flow during the procedure.

Statistical analysis included correlation coefficients and analysis of significance of bronchoscopic and roentgenographic measurements.

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Reprints not available.



Correlation coefficients between bronchoscopic and roentgenographic measurements. Data are summarized for seven groups of 10 examinations each.

RESULTS

Seventy examinations were performed on 65 neonates. Mean gestational age was 32 weeks (range, 24 to 42 weeks), and mean weight at time of examination was 1610 ± 1054 g (range, 540 to 4400 g). Age at time of examination ranged from 30 minutes to 6 weeks.

During the procedure, no ETTs were dislodged. No significant changes were noted in oxygen saturation as measured by pulse oximetry or arterial blood gases. No change in ventilator settings was required after the procedure.

The correlation coefficient between the bronchoscopic and roentgenographic measurements rose from .26 in the first group of 10 examinations to .96 in the final group of 10. The Figure shows the correlation coefficients for sequential examinations; the slope of the graph represents the "learning curve." These data represent the combined experience of three investigators, each of whom performed approximately one third of the studies. The learning curve for each of the investigators was similar and, thus, an individual investigator should achieve a correlation of .95 or greater after approximately 20 studies.

Abnormal airway findings of clinical significance that had not been suspected prior to examination were found in 13 examinations (19%). Clinical significance was defined as findings that altered the patient's management, and these included such diagnoses as

tracheobronchomalacia in two term neonates, necrotizing tracheobronchitis in one extremely premature neonate, plugging of major airways with meconium and with mucus in two neonates each, and early hemorrhagic pulmonary edema in two neonates. Frothy hemorrhagic secretions were noted in the airways in these cases long before they were seen in or suctioned from the ETT. Additional problems that related to ETT position included positioning above a stenotic region in one neonate, occlusion of the ETT orifice by the lateral tracheal wall in two neonates, and ruling out of suspected ETT occlusion in one neonate. Examples of the changes in clinical management included dislodging and suctioning meconium and mucus plugs with the bronchoscope, alteration of ventilation strategy and extreme care to suction only to the end of the ETT in the neonate with necrotizing tracheobronchitis, and the use of increased positive end-expiratory pressure in hemorrhagic pulmonary edema. The results of these interventions produced a dramatic improvement in the ventilatory status of one of the neonates with meconium plugging; more moderate improvements were seen in the other neonates with plugged airways, with gradual improvement in the condition of the neonate with necrotizing tracheobronchitis and prompt resolution of the hemorrhagic pulmonary edema.

COMMENT

This study demonstrates that fiberoptic bronchoscopy is a safe and accurate method for assessment of ETT position and has utility for the detection of significant airway disease that is unsuspected on clinical grounds. Some problems were encountered in the use of the bronchoscope, including difficulty directing the bronchoscope consistently and easily to the desired bronchus, a tendency for blurring of the screen with secretions, and inability to examine the upper lobe bronchi. One error in the early phase of the study was misdiagnosis of the bifurcation of the right main

ductus bronchus for the main carina. No difference in incidence of problems was noted between the two bronchoscopes used.

Although the procedure is relatively rapid (30 to 60 seconds per examination), it demands skilled personnel who may not be available in all neonatal intensive care unit settings. This fact, combined with the relative ease of acquiring a chest roentgenogram, may limit the widespread applicability of this procedure for assessing ETT placement. However, this method could potentially save many neonates from unnecessary repeated roentgen ray exposure.

It is striking that such a high incidence of clinically significant airway problems was found. To our knowledge, there are no reported studies of the prospective use of routine bedside bronchoscopy in all intubated neonates; such a study would appear to be indicated by the above data.

In summary, ultrathin fiberoptic bronchoscopy was found to be a useful diagnostic and therapeutic tool in the intubated neonate. Endotracheal tube position can be reliably confirmed by this method. An important application of bronchoscopy may be for screening for airway disease in intubated neonates.

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Infant Sleep and Bedtime Cereal

Michael L. Macknin, MD; Sharon VanderBrug Medendorp, MPH; Mary C. Maier, MD

• We studied whether feeding infants rice cereal before bedtime promotes their sleeping through the night. One hundred six infants were randomly assigned to begin bedtime cereal feeding (1 tablespoon per ounce in a bottle) at 5 weeks or at 4 months of age. Caretakers recorded the infant's sleep from age 4 to 21 weeks for the 24-hour period per week. Sleeping through the night was defined as sleeping at least 8 consecutive hours, with the majority of time being between the hours of midnight and 6 AM. The results were also reviewed changing the requirement from 10 hours to 6 hours. There was no statistically significant trend or a consistent tendency of one group to have a higher proportion of sleepers than the other. Therefore, feeding infants rice cereal in the bottle before bedtime does not appear to make much difference in their sleeping through the night.

(AJDC. 1989;143:1066-1068)

Folklore suggests that feeding infants solids prior to bedtime increases the duration of uninterrupted sleep. This is somewhat documented in the literature. In a survey of Nebraskan pediatricians and family practitioners, 40% of the respondents agreed that "one advantage of adding solid food to the diet very early is that it helps baby sleep through the night."¹ Several poorly controlled, unrandomized studies suggest that feeding infants solids helps them to sleep through the night.²⁻⁴ Clinical practice shows that many parents use this reasoning to introduce multiple solid foods to infants in the first few months of life.

There is also evidence to suggest that

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feeding of solids prior to bedtime is not related to evening sleep patterns. Recently, an abstract of a randomized controlled clinical trial reported that cereal given before bedtime will not help an infant sleep through the night.⁵ Many poorly controlled, unrandomized studies suggest that the introduction of solid food has no relationship to sleeping through the night.⁶⁻¹¹

The American Academy of Pediatrics Committee on Nutrition suggests that for theoretical reasons the introduction of solid foods should be delayed until an infant is 4 to 6 months old.¹² The theoretical reasons for withholding solid foods until this time include decreasing solute load placed on an immature kidney, avoiding overfeeding and force-feeding, and preventing allergic reaction secondary to immature antigen processing. There are no proved adverse effects of early introduction of cereal into an infant diet.¹³ This study was designed to determine if infant rice cereal given before bedtime will help an infant sleep through the night.

SUBJECTS AND METHODS

Subjects

One hundred six newborns who had a birth weight of over 2.5 kg and were first seen for well-child care at The Cleveland (Ohio) Clinic Foundation Pediatric Primary Care Center before the age of 1 month were eligible for study. Four additional subjects enrolled in the study could not be included in the data analyses because their parents did not complete any cry/fuss diaries. The Pediatric Primary Care Center provides health care to the children of employees of The Cleveland Clinic Foundation. Children were ineligible for study if they were without a consistent caretaker after 6 PM or had congenital anomalies or other illnesses that might significantly impair feeding.

Procedures

At either a prenatal or first well-child visit before the age of 1 month, parents were asked to give verbal informed consent for

participation in a study of infant sleeping patterns. Children were randomly assigned to begin bedtime cereal feeding at 5 weeks of age (early group) or 4 months of age (late group). The parents in both groups were asked to feed their infants only rice cereal, breast milk, and/or formula until 5 months of age.

Beginning at 1 month of age, parents in both groups recorded their infant's periods of crying and fussing each week from noon Tuesday through noon Wednesday on the parental diary of infant behavior devised by Barr et al,¹⁴ an instrument previously validated by 24-hour cry/fuss recordings. They were also asked to record periods of sleeping and quantity or length of feedings in bottle-fed and breast-fed infants. Infants received cereal-thickened feedings, one tablespoon per ounce of breast milk or formula, from a bottle between 6 PM and 9 PM only. The amount of cereal was recorded. At 4 months of age, infants in the second group had rice cereal introduced into their diets in an identical manner. (Note that we do not routinely recommend feeding infants cereal in a bottle. However, we did not want to introduce infant reaction to spoon-feeding as an additional variable in the study.) Both groups of parents continued to record infant cry/fuss, feeding, and sleeping patterns until 5 months of age.

The sample size was chosen to detect a success rate of 25% vs 50% at a significance level of 5%, with 80% power, assuming a 20% noncompletion rate of the study.¹⁵ Success was defined as an infant sleeping 8 consecutive hours, with the majority of the sleeping between midnight and 6 AM.

Randomization of subjects to the two feeding schedules was balanced after every fourth patient in each of the assignment risk strata. Randomization was accomplished by sealed envelopes generated for each risk stratum by the Department of Biostatistics and Epidemiology. The strata were defined by birth weight (2.50 to 3.00 kg, 3.01 to 3.50 kg, 3.51 to 4.00 kg, 4.01 kg or more) and a mother's intention to primarily breast-feed or bottle-feed. Additional variables not included in the randomization were maternal and paternal education (in years), race, number of other children less than 5 years old in the household, household member working

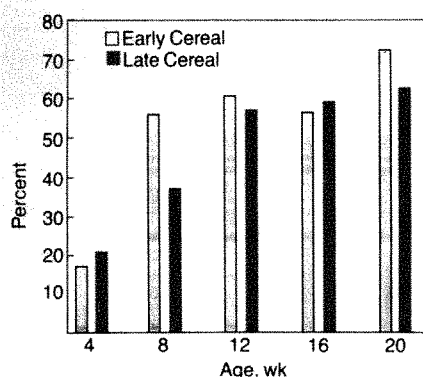


Fig 1.—Proportion of infants sleeping at least 6 consecutive hours, with the majority of the time between midnight and 6 AM. Early cereal represents the group given cereal at 5 weeks of age; late cereal, the group given cereal at 4 months of age.

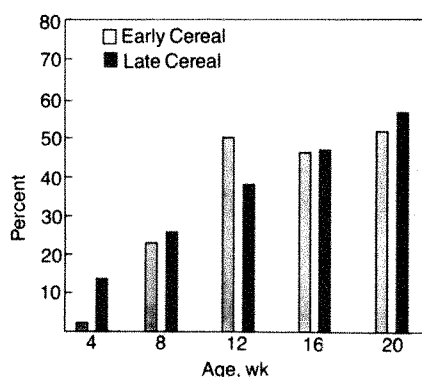


Fig 2.—Proportion of infants sleeping at least 8 consecutive hours, with the majority of the time between midnight and 6 AM. Early cereal represents the group given cereal at 5 weeks of age; late cereal, the group given cereal at 4 months of age.

an evening shift, amount of cereal eaten in 24 hours, weight for height percentile, amount of formula consumed per 24 hours, number of feedings per 24 hours, number of cry/fuss periods per 24 hours, and weight percentile.

The major analysis consisted of a comparison of the proportions of subjects sleeping through the night in the two groups. This comparison was reported specifically when the participants were 4, 8, 12, 16, and 20 weeks of age. These weeks were chosen because they represent roughly the first 5 months of an infant's life and because there were no dramatic week-to-week variations in sleep data. (Weekly data are available on request.)

The χ^2 and Student's *t* tests were used to explore whether the prognostic risk factors (birth weight, type of feeding, maternal education level, etc) were in fact associated with evening sleeping at various times/ages throughout the study period.¹⁶

RESULTS

At baseline (4 weeks of age), the two feeding groups were comparable in parent's intention to primarily breast-feed or bottle-feed (52.7% intended to breast-feed in the early group, 54.9% in the late group). They also had comparable birth weights, maternal and paternal levels of education, number of children under 5 years of age in the household, household members working an evening shift, sex, race, and baseline sleeping patterns.

The data were analyzed for a sleep requirement of both 8 and 6 consecutive hours. Sleeping through the night for both the 8- and 6-hour definitions was

unrelated at weeks 4, 8, 12, 16, and 20 to the level of parental education, number of children in the household less than 5 years of age, household members working an evening shift, breast-feeding versus bottle-feeding, birth weight, gender, and race. Infant sleep patterns were unrelated to the introduction of bedtime cereal in the bottle.

The mean total sleep was 13.8 and 14.2 hours for the early and late groups, respectively, at 4 weeks of age, and 13.8 hours for both groups at 20 weeks of age. The means varied little during the time of the study (13.3 to 14.4 hours in the early group, 13.4 to 14.2 hours in the late group).

The total mean number of sleeping periods diminished in a similar manner in both the early and late groups, respectively (7.2 and 7.4 at 4 weeks, 6.2 and 6.3 at 8 weeks, 5.0 and 5.7 at 12 weeks, 5.2 and 5.0 at 16 weeks, and 4.5 and 5.3 at 20 weeks).

The lengths of the first, second, and third longest duration of sleep were compared for the two groups. At 4 weeks of age, the mean longest durations of sleep for the early and late groups were 4.6 and 5.2 hours, respectively; this increased to 7.1 and 7.0 hours, respectively, at 8 weeks; 8.5 and 8.3 hours, respectively, at 12 weeks; 8.3 and 8.8 hours, respectively, at 16 weeks; and 8.9 and 8.6 hours, respectively, at 20 weeks. Note that while there is a steady increase in the duration of sleep with age, there is no clear difference in sleep duration between the two

groups at any of the time points.

For recording purposes, the 24-hour clock was divided into four 6-hour segments: noon to 6 PM, 6 PM to midnight, midnight to 6 AM, and 6 AM to noon. Along with the length of the longest duration of sleep, the time of day during which the majority of this period occurred was also recorded. In both groups the longest sleep period occurred most often in the midnight to 6 AM time slot. This was true throughout the study period. At 4, 12, and 20 weeks, 69.0%, 71.1%, and 86.2%, respectively, in the early cereal group and 70.4%, 69.0%, and 71.9%, respectively, in the late cereal group experienced the longest sleep duration between midnight and 6 AM.

The proportion of infants sleeping at least 6 consecutive hours was 16.7% and 20.5% in the early and late groups, respectively, at 4 weeks of age; 56.3% and 37.2%, respectively, at 8 weeks of age; 60.5% and 57.1%, respectively, at 12 weeks of age; 56.4% and 58.8%, respectively, at 16 weeks of age; and 72.4% and 62.5%, respectively, at 20 weeks of age (Fig 1).

When the requirement was increased from 6 to 8 consecutive hours of sleep, the proportions at 4 weeks (Fig 2) were 2.4% and 13.6% in the early and late groups, respectively. With the introduction of bedtime cereal at 5 weeks, 2.0% of the early cereal group and 8.7% of the late cereal group met the criteria. At 8 weeks, the criteria were met by 22.9% and 25.6% of the infants; at 12 weeks, 50.0% and 38.1% of the infants; at 16 weeks, 46.2% and 47.1% of the infants; and at 20 weeks, 51.7% and 56.3% of the infants in the early and late cereal groups, respectively. Although the proportion increased with age, there were no statistically significant differences for either definition in the proportion of infants sleeping through the night between the early and late cereal groups during any week studied from age 4 to 21 weeks, except at age 7 weeks for the 8-hour definition. At age 7 weeks, 27.9% of the late-feeding group and 8.5% of the early-feeding group ($P < .05$) slept through the night. Since this difference at 7 weeks of age was not part of a trend or consistent tendency it must be reviewed and interpreted in this context.

COMMENT

Our findings support previous studies suggesting that infants' ability to sleep through the night is a developmental and adaptive process that occurs regardless of the timing of introduction of cereal.^{7,8}

Several uncontrolled unrandomized studies have been done to study infant sleep patterns.^{4-10,17} Data recorded in previous studies of infant sleep patterns have primarily been done with unvalidated instruments, with the exception of Kleitman and Engelmann's¹⁸ use of actogram recorders on cribs of infants. Parmelee et al⁷ studied 46 infants during the first 16 weeks of life and found that a diurnal cycle was evident in the first 2 weeks of life, becoming statistically significant by 8 weeks of age. Solid foods were introduced in an uncontrolled manner, and the time of their introduction was found not to correlate with increased sleeping times. These findings are consistent with our own. Beal⁸ states that of infants fed solids in the first 4 weeks of life, 28% were already sleeping through one night feeding prior to the introduction of solid foods. She believes that the ability to sleep through the night is a stage reached in the second month of life regardless of diet composition. Other articles support these findings.^{6,7,9,10}

There are several uncontrolled, anecdotal studies supporting the introduction of solid foods to help infants sleep through the night. These include a study by Glazier² who felt that infants fed solids had "fewer faulty habits, including sleeping difficulties." Sackett³ designed a three-meal-a-day plan eliminating nighttime feedings. Wilkinson and Davies⁴ claimed to reach higher levels of contentment among infants receiving solid foods.

Previous studies have also compared sleeping patterns among breast-fed and bottle-fed infants.¹⁸ The breast-fed infants continued to have frequent nighttime wakings and fewer total hours of sleep per day during the first 2 years of life. This has also been noted by Keane et al.⁵ In our study the infants were classified at the time of enrollment into breast-feeding or bottle-feeding groups based on the mother's intention. The data based on this intention did not support a difference in sleeping patterns for breast-fed and bottle-fed infants. This lack of difference may have been due to a difference in definitions of a breast-fed or bottle-fed infant. Perhaps enough mothers changed their predominant feeding method during the study to obscure differences in sleeping patterns between the two groups. Also, the specific method of breast-feeding, tradi-

tional (every 2 to 4 hours) vs LeLeche (every 1 hour or on demand) was not controlled for. The timing of feedings was left to the mother's discretion. There was less variability for all infants in total time slept per day and in what segment of the day the longest sleep period occurred as the infants matured, whether they were fed cereal early or late, and whether they were breast-fed or bottle-fed.

The majority of infants in our study slept 6 consecutive hours at night by 12 weeks of age and 8 consecutive hours at night by 20 weeks of age. The timing of the introduction of cereal in the bedtime bottle was not related to total hours of sleep, number of sleeping periods, longest duration of sleep, or the time interval in which sleep occurred. In addition, no relationship was found between sleeping through the night and introduction of cereal at 5 weeks vs 4 months of age. The results of our study refute the practice of introducing bedtime cereal in an infant's bottle to promote sleeping through the night.

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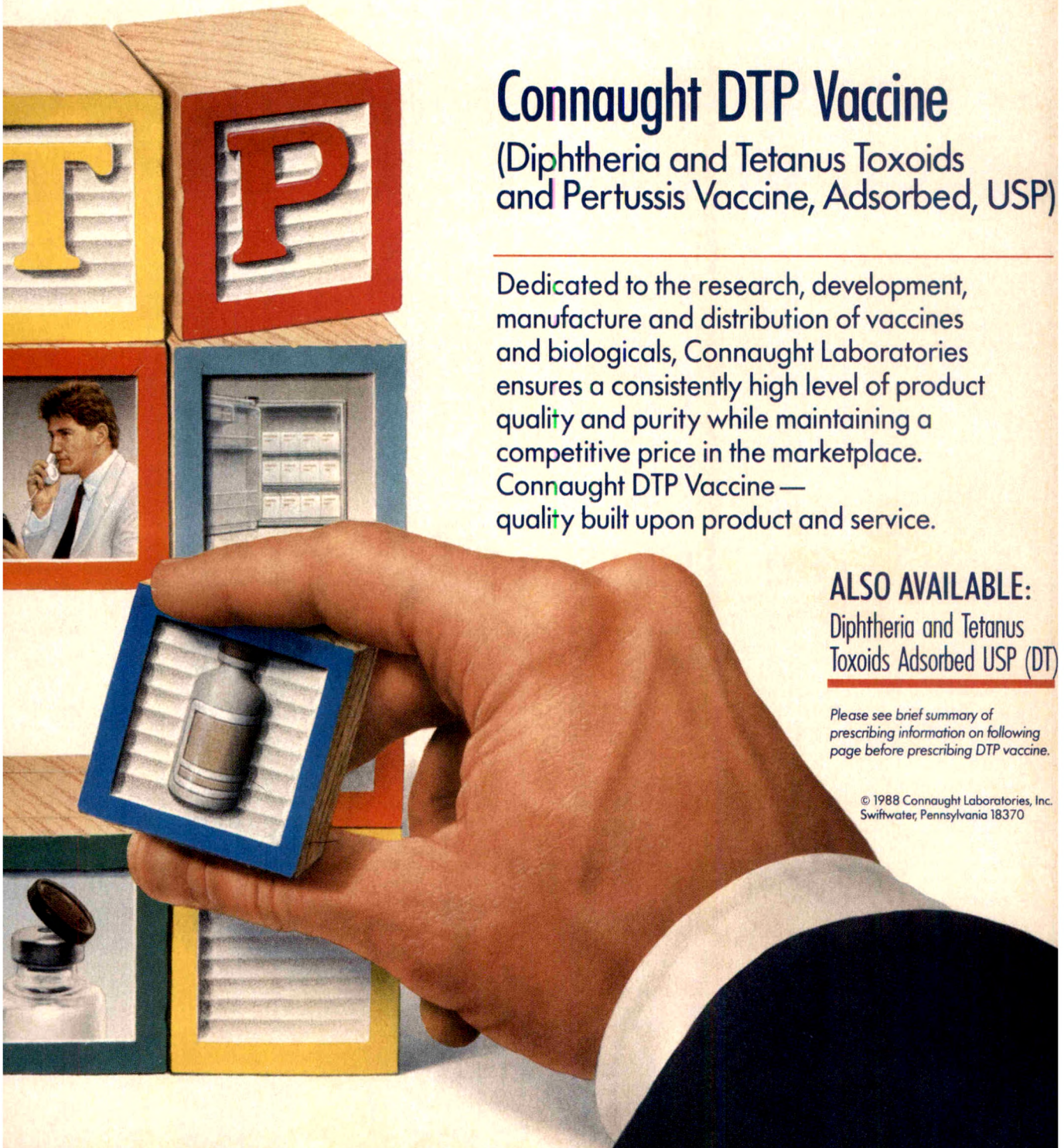
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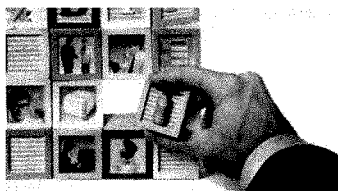
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INDICATIONS AND USAGE: For active immunization of infants and children to age 7 years against diphtheria, tetanus and pertussis (whooping cough) simultaneously. DTP is recommended for primary immunization of infants and children up to 7 years of age. However, in instances where the pertussis vaccine component is contraindicated, or where the physician decides that pertussis vaccine is not to be administered, Diphtheria and Tetanus Toxoids Adsorbed (For Pediatric Use) should be used. Immunization should be started at 6 weeks to 2 months of age and be completed before the seventh birthday.

CONTRAINDICATIONS: Persons 7 years of age and older must NOT be immunized with Pertussis vaccine.

Absolute contraindications.

1. Allergic hypersensitivity to any component of the vaccine.
2. Fever of 40.5°C (105°F) or greater within 48 hours.
3. Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
4. Persisting, inconsolable crying lasting 3 hours or more or an unusual, high-pitched cry occurring within 48 hours.
5. Convulsion(s) with or without fever occurring within 7 days.
6. Encephalopathy occurring within 7 days; this includes severe alterations in consciousness with generalized or focal neurologic signs.

The presence of a neurologic condition characterized by changing developmental or neurologic findings, regardless of whether a definitive diagnosis has been made, is also considered an absolute contraindication to receipt of pertussis vaccine, because administration of DTP may coincide with or possibly even aggravate manifestations of the disease. Such disorders include uncontrolled epilepsy, infantile spasms, and progressive encephalopathy.

Use of this product is also contraindicated if the child has a personal or family history of a seizure disorder. However, the ACIP does not accept family histories of convulsions or other central nervous system disorders as contraindications to pertussis vaccination.

IT IS ALSO A CONTRAINDICATION TO ADMINISTER DTP TO INDIVIDUALS KNOWN TO BE SENSITIVE TO THIMEROSAL. IN ANY CASE, EPINEPHRINE INJECTION (1:1000) MUST BE IMMEDIATELY AVAILABLE SHOULD AN ACUTE ANAPHYLACTIC REACTION OCCUR DUE TO ANY COMPONENT OF THE VACCINE.

Elective immunization procedures should be deferred during an outbreak of poliomyelitis.

WARNINGS: This vaccine must NOT be used for immunizing persons 7 years of age and older.

IMMUNIZATION SHOULD BE DEFERRED DURING THE COURSE OF ANY ACUTE ILLNESS. THE OCCURRENCE OF ANY TYPE OF NEUROLOGICAL SYMPTOMS OR SIGNS, INCLUDING ONE OR MORE CONVULSIONS (SEIZURES) FOLLOWING ADMINISTRATION OF THIS PRODUCT IS AN ABSOLUTE CONTRAINDICATION TO FURTHER USE. USE OF THIS PRODUCT IS ALSO CONTRAINDICATED IF THE CHILD HAS A PERSONAL OR FAMILY HISTORY OF A SEIZURE DISORDER.

THE PRESENCE OF ANY EVOLVING OR CHANGING DISORDER AFFECTING THE CENTRAL NERVOUS SYSTEM IS A CONTRAINDICATION TO ADMINISTRATION OF DTP REGARDLESS OF WHETHER THE SUSPECTED NEUROLOGICAL DISORDER IS ASSOCIATED WITH OCCURRENCE OF SEIZURE ACTIVITY OF ANY TYPE.

The administration of DTP to children with proven or suspected underlying neurological disorders, must be decided on an individual basis. Please refer to ACIP recommendations for the following categories of patients:

1. Infants as yet unimmunized who are suspected of having underlying neurologic disease.
2. Infants and children with neurologic events temporally associated with DTP.
3. Incompletely immunized children with neurologic events occurring between doses.
4. Infants and children with stable neurologic conditions.
5. Children with resolved or corrected neurologic disorders.

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. Short-term (less than 2 weeks) corticosteroid therapy or intra-articular, intra-ocular, or tendon injections with corticosteroids should not be immunosuppressive. Although no specific studies with pertussis vaccine are available, if immunosuppressive therapy will be discontinued shortly, it would be reasonable to defer immunization until the patient has been off therapy for one month; otherwise, the patient should be vaccinated while still on therapy.

Persons receiving immunosuppressive therapy, a recent injection of immune globulin, or having an immunodeficiency disorder, may not generate an adequate immunologic response to the DTP vaccine.

DTP should not be given to infants or children with any coagulation disorder that would contraindicate intramuscular injection, unless the potential benefit clearly outweighs the risk of administration.

The simultaneous administration of DTP, oral polio virus vaccine (OPV), and/or measles-mumps-rubella vaccine (MMR) has resulted in seroconversion rates and rates of side effects similar to those observed when the vaccines are administered separately. Please refer to ACIP recommendations.

PRECAUTIONS

GENERAL

Epinephrine injection (1:1000) must be immediately available should an acute anaphylactic reaction occur due to any component of the vaccine.

Prior to an injection of any vaccine, all known precautions should be taken to prevent side reactions. This includes a review of the patient's history with respect to possible sensitivity and any previous adverse reactions to the vaccine or similar vaccines (see CONTRAINDICATIONS), and a current knowledge of the literature concerning the use of the vaccine under consideration.

The vial of vaccine should be vigorously shaken to ensure a proper suspension of the antigen and adjuvant.

Special care should be taken to ensure that the injection does not enter a blood vessel.

A separate sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another.

ADVERSE REACTIONS

Not all adverse events following administration of DTP are causally related to DTP vaccine.

Adverse reactions which may be local and include pain, erythema, heat, edema and induration with or without tenderness, are common after the administration of vaccines containing diphtheria, tetanus, or pertussis antigens. Some data suggest that febrile reactions are more likely to occur in those who have experienced such responses after prior doses. However, these observations were not noted by Barkin, R.M., et al. Occasionally, a nodule may be palpable at the injection site of adsorbed products for several weeks. Sterile abscesses at the site of injection have been reported (6-10 per million doses).

Mild systemic reactions, such as fever, drowsiness, fretfulness, and anorexia, occur quite frequently. These reactions are significantly more common following DTP than following DT, are usually self-limited, and need no therapy other than, perhaps, symptomatic treatment (e.g., antipyretics). Rash, allergic reactions, and respiratory difficulties, including apnea, have been observed.

Moderate to severe systemic events, such as fever of 40.5°C (105°F) or higher, persistent, inconsolable crying lasting 3 hours or more, unusual high-pitched crying, collapse, or convulsions, occur relatively infrequently. More severe neurologic complications, such as a prolonged convulsion or an encephalopathy, occasionally fatal, have been reported to be associated with DTP administration.

Approximate rates for adverse events following receipt of DTP vaccine (regardless of dose number in the series) are indicated in Table 1.

TABLE 1. Adverse events occurring within 48 hours of DTP immunizations

Event	Frequency*
Local	
Redness	1/3 doses
Swelling	2/5 doses
Pain	1/2 doses
Mild/moderate systemic	
Fever >38°C (100.4°F)	1/2 doses
Drowsiness	1/3 doses
Fretfulness	1/2 doses
Vomiting	1/15 doses
Anorexia	1/5 doses
More serious systemic	
Persistent, inconsolable crying (duration ≥3 hours)	1/100 doses
High-pitched, unusual cry	1/900 doses
Fever ≥40.5°C (≥105°F)	1/330 doses
Collapse (hypotonic-hyporesponsive episode)	1/1,750 doses
Convulsions (with or without fever)	1/1,750 doses
Acute encephalopathy†	1/110,000 doses
Permanent neurologic deficit†	1/310,000 doses

*Number of adverse events per total number of doses regardless of dose number in DTP series.

†Occurring within 7 days of DTP immunization.

The frequency of local reactions and fever following DTP vaccination is significantly higher with increasing numbers of doses of DTP, while other mild to moderate systemic reactions (e.g., fretfulness, vomiting) are significantly less frequent. If local redness of 2.5 cm or greater occurs, the likelihood of recurrence after another DTP dose increases significantly.

Although there are uncertainties in the reported studies, recent data suggest that infants and young children who have had previous convulsions (whether febrile or nonfebrile) are more likely to have seizures following DTP than those without such histories.

Rarely, an anaphylactic reaction (i.e., hives, swelling of the mouth, difficulty breathing, hypotension, or shock) has been reported after receiving preparations containing diphtheria, tetanus, and/or pertussis antigens.

Sudden infant death syndrome (SIDS) has occurred in infants following administration of DTP. A large case-control study of SIDS in the United States showed that receipt of DTP was not causally related to SIDS. It should be recognized that the first three primary immunizing doses of DTP are usually administered to infants 2-6 months old and that approximately 85% of SIDS cases occur at ages 1-6 months, with the peak incidence occurring at 6 weeks-4 months of age. By chance alone, some SIDS victims can be expected to have recently received vaccine.

Onset of infantile spasms has occurred in infants who have recently received DTP or DT. Analysis of data from the NCS on children with infantile spasms showed that receipt of DTP or DT was not causally related to infantile spasms. The incidence of onset of infantile spasms increases at 3-9 months of age, the time period in which the second and third doses of DTP are generally given. Therefore, some cases of infantile spasms can be expected to be related by chance alone to recent receipt of DTP.

Reporting of Adverse Events

Reporting by parents and patients of all adverse events occurring within 4 weeks of antigen administration should be encouraged.

The following illnesses have been reported as temporally associated with the vaccine; neurological complications including cochlear lesion, brachial plexus neuropathies, paralysis of the radial nerve, paralysis of the recurrent nerve, accommodation paresis, and EEG disturbances with encephalopathy. In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid, tetanus toxoid should be considered as a possible etiology.

Product information as of July, 1986



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Educational Interventions



Hugh D. Allen, MD, Columbus, Ohio
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Larrie W. Greenberg, MD, Washington, DC

Purpose.—This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.

Editorial Comment.—*This article advocates a careful, prospectively planned approach to curriculum development and its evaluation. The authors applied their approach to an important topic that involves pediatrics and medicine. This is how medical educational research should be done.*—H.D.A.

A Sexually Transmitted Diseases Curriculum in Adolescent Medicine

Jennifer Johnson, MD; J. Dennis Fortenberry, MD; Efstratios Demetriou, MD;
Jana Gober Zimmerman, MS; Robert F. Hill, PhD; Philip J. Rettig, MD

• We conducted a needs assessment and developed and evaluated a model curriculum on sexually transmitted diseases (STDs) for house officers on an adolescent medicine rotation. Residents thought it important for physicians to acquire skill in treating STDs during residency (mean rating, 4.4 on a five-point scale) and were willing to provide medical care for adolescents likely to have an STD (mean rating, 4.4). Knowledge was measured before and after presentation of both of the two curriculum levels. There were significant increases in knowledge after each level, with a mean increase of 4.4 (of 50 possible) points for level 1 and a mean increase of 1.8 (of 38 possible) points for level 2. This improved knowledge about STDs should reflect increased competence and enhanced willingness to treat STDs in adolescents.

(AJDC. 1989;143:1073-1076)

Sexually transmitted diseases (STDs) contribute substantially to adolescent morbidity; the highest rates of many STDs are found in sexually active 15- to 19-year-olds.¹ From 3% to 27% of adolescent females have cervical *Chlamydia trachomatis* infections^{2,3}; 7% to 10% are infected with *Neisseria gonorrhoeae*.^{4,5} Even in an adolescent clinic with a low prevalence of gonorrhea (<1% of cultures positive), STDs were an identified patient concern in 10% of all visits.⁶ Thus, physicians who provide medical care for adolescents should be educated about STDs; however, formal training in diagnosis and management of STDs is offered in only a few medical schools and residency programs.⁷ Only 18% of respondents to a 1980 survey on clinical training in venereology in US and Canadian medical schools rated

their program as adequate.⁷ Only 1 of 117 pediatric programs surveyed in 1980 offered formal training in STDs to house staff; 23% of internal medicine residency programs did so.⁷ A survey conducted in 1983 revealed that a majority of pediatric program graduates expressed satisfaction with residency lectures and training about STDs. However, 14% of these graduates had never diagnosed or treated gonorrhea, and only 13% had done so more than 20 times.

More than half of pediatric residency programs incorporate a training experience in adolescent medicine.⁸ Although the adolescent medicine rotation provides an excellent opportunity for training physicians to diagnose and treat STDs, to our knowledge there have been no reports of formal STD programs within this setting. We describe the development and implementation of a model STD curriculum for house staff participating in an adolescent medicine rotation.

METHODS

Adolescent Medicine Rotation

House staff from the departments of pediatrics and medicine at the University of Okla-

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From the Departments of Pediatrics (Drs Johnson, Hill, and Rettig) and Medicine (Dr Fortenberry), University of Oklahoma Health Sciences Center, Oklahoma City; the Departments of Pediatrics, Boston (Mass) City Hospital and Boston University School of Medicine (Dr Demetriou); and the Consortium Internship in Clinical Psychology, University of Texas Southwestern Medical Center and Terrell State Hospital, Dallas (Ms Zimmerman).

Presented in part at the 26th Annual Meeting of the Southern Society for Pediatric Research, New Orleans, La, January 28, 1987; the 14th Annual Meeting of the Society for Adolescent Medicine, Seattle, Wash, March 19, 1987; and the 29th Annual Meeting of the Ambulatory Pediatric Association, Washington, DC, May 2, 1988.

Reprint requests to Adolescent Medicine Section, CHO 4N237, PO Box 26901, Oklahoma City, OK 73190 (Dr Johnson).

homa Health Sciences Center, Oklahoma City, participate in 1-month rotations on the adolescent medicine service at Oklahoma Children's Memorial Hospital. Each pediatric house officer rotates on the service annually. Medicine house staff rotate twice on adolescent medicine during their 3 years of residency. During any given month, 7 to 10 house officers are assigned to the adolescent medicine service. Approximately 55 pediatric residents and 45 residents in internal medicine serve in the program annually.

During the rotation, residents have primary responsibility for patients 14 to 21 years of age, including ambulatory patients presenting to the adolescent clinic or the emergency department, and all nonsurgical adolescent inpatients. Each year there are approximately 12 000 outpatient visits to the adolescent clinic, 2000 visits to the emergency department, and 600 medical inpatients. During the study period (1984 to 1987), 15% to 20% of primary diagnoses in the clinic were related to STDs (most commonly vaginitis and cervicitis). Approximately 25% of primary diagnoses involved reproductive concerns (contraception and pregnancy). These diagnoses reflect the preponderance of female patients (75%) in the clinic. About 13% of visits by males were related to STDs. Approximately 10% of inpatient admissions during the study period were for pelvic inflammatory disease.

Faculty supervision of house staff is provided by two pediatricians and one internist specializing in adolescent medicine as well as a pediatric infectious diseases specialist. A faculty member is always available on site for individual consultation with residents during clinic hours.

Prior to implementation of the model STD curriculum, residents received approximately 4 hours of formal instruction on STDs annually. Senior internal medicine residents participating in an elective infectious diseases rotation had the opportunity to attend the Oklahoma City-County STD Clinic for 4 hours weekly during that period.

Needs Assessment

During the first year of the project (1984-1985), a needs assessment questionnaire was distributed to residents during their adolescent medicine rotation. Physicians were asked to provide demographic data anonymously (including level of training and previous STD and adolescent medicine experience) and to rate the importance of competence, current self-perceived competence, and interest in learning about 16 STDs and related topics. These topics are included in the learning objectives of the STD curriculum (see below). Ratings on a five-point Likert scale were obtained for importance, competence, and interest for each topic. A

rating of 1 was lowest ("not") and a rating of 5 was highest ("very") in each scale, eg, for the "importance" scale, 1 = not important, 5 = very important. (The questionnaire is available on request.)

STD Curriculum

Eighteen learning objectives were identified and stratified into two levels. Nine basic objectives were included in level 1 and presented to house staff during the second year of the project (1985-1986). Level 1 focused on physical and laboratory assessment of patients with suspected STDs, special concerns regarding adolescents with STDs, and common STD syndromes, such as vaginal discharge and mucopurulent cervicitis. During the third year (1986-1987), material was added to the level 1 content. The learning objectives for level 2 consisted of less-common STDs, such as epididymitis and cutaneous syndromes, and specialized topics, including STDs in children and in homosexual patients.

Formats utilized in presentation of the curriculum to house staff included lectures, discussions, videotapes, a plastic teaching model of the female pelvis, laboratory demonstrations, and a manual written by one of the project directors. Attending faculty on the inpatient service lectured and led discussions on attending rounds for approximately 6 hours each month. One of the curriculum project directors (P.J.R.), a pediatric venereologist, attended one half day weekly in the adolescent clinic. House staff were encouraged to present unusual or problematic cases to him.

Residents participated in an STD training session at the beginning of the rotation. This 1½-hour overview used a videotape ("Pelvic Examination of the Female with Sexually Transmitted Disease," provided by the Centers for Disease Control, Atlanta, Ga) and a plastic pelvic teaching model to introduce necessary clinical skills. Discussion emphasized the need to consider STDs in adolescents within the context of developmental issues and risk-taking behaviors. The session was completed by demonstration of potassium hydroxide, normal saline wet preparation, and Gram's stain smear techniques for evaluation of genital secretions. Teaching slides illustrating these techniques were reviewed using a multiheaded microscope.

A manual entitled *STDs: Specially Teen-aged Diseases* was written by one of us (P.J.R.) in a problem-oriented format encompassing level 1 learning objectives. This manual, which emphasizes the biologic, psychosocial, and legal aspects of STDs that are unique to adolescents, was distributed to each resident at the beginning of the rotation. (The manual is available for a nominal fee from one of us [J.J.].)

Implementation

Residents on the adolescent medicine rotation between July 1, 1985, and June 30, 1986, participated in the level 1 curriculum. Level 2 material was then introduced, so that all residents on the rotation between July 1, 1986, and June 30, 1987, were presented with both the level 1 and the level 2 curricula.

Knowledge Assessment

Pretests and posttests were administered to assess learning attributable to the curriculum. K-type multiple-choice questions were developed in part from materials used in Centers for Disease Control STD training courses and by the Oklahoma State Department of Health; additional original questions relevant to adolescent medicine concerns were formulated. The items were evaluated for validity and difficulty by administering them to selected third-year residents and infectious disease fellows. Of items chosen for use in program evaluation, 50 pertained to level 1 learning objectives and 38 were relevant to level 2. Ten items for the level 1 test and 4 for the level 2 test included a pictorial component. To assess changes in knowledge about the level 1 material, the 50 items were administered to house staff in each month of the level 1 curriculum in a pretest-posttest format. Questions on the pretest were randomly reordered to form the posttest. The examination was administered in a split-half design to evaluate the influence of pretesting on posttest scores. Half of the residents were randomly assigned to take the pretest at the beginning of the rotation; all took the posttest at the end of the rotation. Residents were asked to identify themselves by birth date and social security number only. During the second year of the project, when material related to both level 1 and level 2 was presented, all residents completed both the pretest and posttest, consisting of the 38 items related to level 2 learning objectives. Several items were revised after the first four testing cycles. (The tests are available on request.) Approval to administer the tests was obtained from the Institutional Review Board of the University of Oklahoma Health Sciences Center.

Data Analysis

Needs Assessment.—Statistical analysis was performed using the Statistical Analysis Systems package, version 5.16,⁹ and using the ABstat statistical package, release 4.¹⁰ A composite "interest" index (maximum, 100 points) was derived from interest ratings for the 16 STD-related topics. Independent *t* tests were used as appropriate.

Knowledge Assessment.—Raw scores of examinations taken by pediatric and medicine residents in each year of the project

Table 1.—Pretest and Posttest Scores						
	Possible Points	Pretest		Posttest		P
		Mean (SD) Score	No. of Subjects	Mean (SD) Score	No. of Subjects	
Level 1*						
Pretested subjects	50	24.0 (3.9)	51	26.9 (5.1)	50	.0001
Nonpretested subjects	50	28.1 (5.0)	50	...
Level 2						
Original version	38	22.7 (3.6)	33	24.3 (3.1)	32	.004
Revised version	38	17.7 (3.4)	61	19.7 (3.5)	59	.001

*Subjects who had taken the pretest did not score higher on the posttest than subjects who had not taken the pretest ($P = .23$).

Table 2.—Scores of Medicine and Pediatric House Staff (Level 1)						
	Possible Points	Medicine		Pediatrics		P
		Mean (SD) Score	No. of Subjects	Mean (SD) Score	No. of Subjects	
Pretest	50	23.6 (4.0)	27	24.5 (3.8)	24	.43
Posttest	50	28.7 (5.0)	45	26.5 (4.9)	56	.026

were analyzed separately using the Statistical Analysis Systems package, version 5.16. For level 1, scores for the six learning objectives, represented by at least five questions on the test, were further analyzed. All P values reported are for independent t tests, except for comparisons of individual residents with themselves, when paired t tests were used.

Approval to conduct the study was obtained from the Institutional Review Board of the University of Oklahoma Health Sciences Center.

RESULTS

Needs Assessment

Of 73 residents on the rotation during the needs assessment phase, 64 (88%) completed the questionnaire. Thirty-four were pediatric and 30 were medicine residents. There were 28 first-year, 19 second-year, and 17 third-year residents. Forty-five were men. About half (33 residents) had previously served on the adolescent medicine service. Residents thought it was quite important for physicians to increase their skill in treating patients with STDs during residency training (mean rating, 4.4) and were quite willing to provide health care for adolescents with suspected STDs (mean rating, 4.3). General self-perceived clinical competence in

managing STDs was somewhat lower (mean rating, 3.6), as was the level of interest in learning about STDs (mean rating, 3.9). The mean perceived competence rating was higher for level 1 (3.7) than for level 2 (2.7) topics. Analysis of ratings for individual learning objectives revealed that residents believed both level 1 and level 2 objectives were quite important (mean ratings, 4.6 and 4.2, respectively) and that they were interested in learning about both sets of objectives (mean rating, 3.8 for each set of objectives). Acute dysuria in females, epididymitis, and genital ulcers were of particular interest. The overall "interest" index of pediatric residents did not differ from that of medicine residents (77.9 vs 80.4, $P = .48$). Female medicine residents had a significantly higher mean interest index (92.8) than both male medicine residents (76.2, $P < .02$) and female pediatric residents (76.7, $P < .01$).

Knowledge Assessment

Level 1.—During the 1985-1986 academic year, 45 medicine and 56 pediatric residents participated in the level 1 curriculum; 41 were in their first postgraduate year. Pretest and posttest results are shown in Table 1. The mean score

increase calculated by paired t test was 4.4 points ($P = .0001$).

Scores of pediatric and medicine house staff are compared in Table 2. Although pretest scores did not differ, posttest scores of medicine residents were higher than those of pediatric residents. Scores of first-year residents did not differ from those of second- and third-year residents on either the pretest ($P > .06$) or posttest ($P > .08$).

Level 2.—Fifty medicine and 44 pediatric residents participated during the 1986-1987 academic year; 35 were first-year residents. Two residents did not complete the posttest. Test scores are found in Table 1. The mean score increase as calculated by paired t test was 1.8 points ($P < .0001$). Residents who had participated in the level 1 curriculum did not score differently on either the pretest or posttest than those who had not participated ($P > .15$). There was no relationship between mean score and medical specialty ($P > .40$) or level of training ($P > .19$).

COMMENT

It has been suggested that pediatric residency programs lack a core curriculum built around educational objectives¹¹ and that these programs may underemphasize education by stressing training.¹¹ The model STD curriculum described herein was developed and implemented according to specified learning objectives. It represents an effort to rectify previously described deficiencies in house staff education about STDs.⁷ Data collected during needs assessment indicated that house staff were interested in providing care for adolescents with STDs. There was a discrepancy between self-assessed competency in managing STDs and the perceived importance of these skills. Residents were more interested in learning about less commonly seen conditions. These findings are consistent with previously reported data.¹²

This curriculum differs from other educational programs developed for house staff in that knowledge change associated with implementation of the curriculum was evaluated. The examinations did not assess clinical skills, nor did they reassess attitudes toward treating patients with STDs. Comparison of mean pretest and posttest scores

revealed a modest but significant improvement in posttest scores that, in the level 1 testing, was shown not to be attributable to recall from the pretest. It is possible that the increase in posttest scores would have been greater had the pretest been less difficult. Also, the test may have underemphasized areas in which the most significant objective learning occurred. Although the curriculum was the primary intervention that might be expected to influence posttest scores, a learning effect due solely to clinical practice in evaluating patients with STDs might contribute to the increase in posttest scores. However, upper-level residents who had a rotation in adolescent medicine before the curriculum was presented did not score higher on pretests than did first-year residents. This suggests that these residents had either not acquired significant knowledge about STDs as measured by the test during their previous rotation or that a knowledge increase had occurred but was no longer mea-

surable at the beginning of the subsequent adolescent medicine rotation. It would be desirable to assess the persistence of the knowledge changes reported herein.

Level 1 posttest scores of medicine residents were slightly but significantly higher than those of pediatric residents, although pretest scores did not differ. This difference did not persist on the level 2 test. Medicine residents as a group had not been more interested in learning about STDs in the needs assessment. It is possible that personal attributes and experiences of medicine residents enabled them to learn more effectively from part of the curriculum. A previous study¹³ found that medicine residents in our training program were more likely than pediatric house staff to have experimented with drugs, to have begun sexual intercourse before age 21 years, and to have experienced an unplanned pregnancy.

It has been suggested that self-assessed competence in reproductive and

adolescent medical issues may be factors in the willingness of physicians to provide care for adolescents.¹⁴ A 1-month adolescent medicine rotation has been reported to improve pediatric residents' self-assessed competence.¹⁵ Experience in an adolescent clinic over an extended period for a total of approximately 30 hours, however, was not found to increase the interest or self-assessed skill of the pediatric house staff in adolescent medicine.¹⁶ Utilizing a thoughtfully planned and implemented curriculum within an adolescent medicine rotation should not only increase knowledge, as did our STD curriculum, but also may enhance physician willingness and confidence in serving as care providers for adolescents.

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In Other AMA Journals

ARCHIVES OF INTERNAL MEDICINE

Infectious and Toxic Syndromes From Fish and Shellfish Consumption

Janet Eastaugh, MD, Suzanne Shepherd, MD (*Arch Intern Med*. 1989;46:1735-1740)

The New Medical Practice Environment

Charles O. Hersheyk, MD; Margaret H. McAloon, MD; Dennis A. Bertram, MD, MPH, ScD (*Arch Intern Med*. 1989;46:1745-1749)

Acute Changes in Renal Function Associated With Deferoxamine Therapy

Gideon Koren, MD; Yedidia Bentur, MD; Dawn Strong, PharmD; Elizabeth Harvey, MD; Julia Klein, MSc; Reuben Baumal, MD, PhD; Stephen P. Spielberg, MD, PhD; Melvin H. Freedman, MD

• In three patients who received intravenous deferoxamine there was a twofold to eightfold increase in plasma creatinine level and a parallel decrease in creatinine clearance that resolved when treatment with the drug was discontinued. In two thalassemic patients, diuresis was evident by urine output exceeding fluid intake. The mechanism was studied in dogs that exhibited an acute and significant decrease in inulin and para-aminohippuric acid clearances induced by intravenous deferoxamine. Saline diuresis could prevent the decrease in the glomerular filtration rate but not the decrease in renal blood flow caused by deferoxamine. Deferoxamine induced an acute increase in the fractional excretion of sodium, potassium, chloride, phosphate, and urate, which may explain the relative diuresis observed in two of the patients. In a subsequent experiment, ferrioxamine induced an increase in the fractional excretion of sodium and chloride but did not affect the glomerular filtration rate and renal blood flow. Our studies suggest that adequate hydration may be needed to preserve renal hemodynamics during intravenous deferoxamine therapy. Repeated measurements of renal function should accompany treatment with this agent. (AJDC. 1989;143:1077-1080)

Deferoxamine is widely used as a chelator in cases of acute or chronic iron overload.¹ In acute iron overload due to

accidental ingestion of iron pills, deferoxamine is generally administered for a few days, and patients with transfusion-dependent thalassemia are treated by nightly subcutaneous infusions of deferoxamine using a battery-powered syringe pump. For many years this mode of therapy has been assumed to be safe; however, recent studies from our service have documented serious neurotoxicity induced by long-term deferoxamine therapy, with transitory or permanent hearing and visual losses.^{2,3} We report acute changes in renal function observed in three patients receiving intravenous deferoxamine infusions. A subsequent animal study confirmed the causal relationship between deferoxamine and renal adverse effects.

PATIENT REPORTS

In April 1987, three cases of acute renal failure were documented during intravenous deferoxamine therapy at The Hospital for Sick Children, Toronto, Canada. Patients 1 and 2 suffered from thalassemia major and were treated for several years with nightly subcutaneous infusions of deferoxamine to remove transfusional iron overload. Because of their poor compliance with this regimen and increasing evidence of cumulative iron burden, they were hospitalized for intensive deferoxamine therapy, 10 mg/kg per hour, 18 hours per day, for 7 days. Patient 3, a 2-year-old girl, was treated with deferoxamine for short-term ingestion of ferrous fumarate tablets.

PATIENT 1.—A 21-year-old Portuguese man (67 kg) with thalassemia major had begun subcutaneous deferoxamine therapy in 1980. Despite this, congestive heart failure developed in 1983, and he was given digoxin hydrochlorothiazide and spironolactone. Prior to admission he had been receiving monthly blood transfusions and was given subcutaneous deferoxamine, 10 mg/kg per hour, five nights per week. Because his serum ferritin level 4 weeks prior to admission was 7976 μ g/L, he was admitted for daily intravenous deferoxamine infusions.

On admission, serum laboratory values were as follows: ferritin, 5300 μ g/L (normal range, 16 to 300 μ g/L); creatinine, 93 μ mol/L;

urea nitrogen, 8.2 mmol/L; hematocrit 0.412; and glucose, 6.4 mmol/L. He had an estimated serum osmolality of 277 mmol/kg. Intravenous deferoxamine therapy was begun at a dosage of 10 mg/kg per hour given in 250 mL of saline for 18 hours daily. The infusions were associated with abdominal pain radiating to his back and nausea and vomiting; however, his systemic blood pressure and heart rate were stable throughout deferoxamine therapy. Overall, his urine output was twice his fluid intake from day 3 to day 1 of deferoxamine therapy. Creatinine clearance decreased during his deferoxamine therapy (Fig 1), and on the 13th day of the protocol he had the following serum laboratory values: creatinine, 262 μ mol/L (Fig 2) urea nitrogen, 20.6 mmol/L; ferritin, 446 μ g/L; and glucose, 7.4 mmol/L; his weight was 62.3 kg. Deferoxamine therapy was discontinued, and on day 14 his serum glucose level was 17.9 mmol/L; serum osmolality, 281 mmol/kg; and urine osmolality, 417 mmol/kg. Over the following 5 days the serum creatinine and urea nitrogen levels began to decline, and on discharge the serum creatinine level was 77 μ mol/L and the urea nitrogen level was 10.4 mmol/L, similar to the value before high-dose deferoxamine therapy was started (Fig 2).

PATIENT 2.—An 18-year-old Chinese man (57 kg) with thalassemia major was admitted for daily intravenous infusion of deferoxamine due to increasing serum ferritin concentrations. Prior to admission he had been receiving nightly deferoxamine, 10 mg/kg per hour, subcutaneously and ascorbic acid, 100 mg/d. Despite therapy his serum ferritin level on admission was greater than 14 000 μ g/L, which was postulated to represent poor compliance with his home deferoxamine therapy. Admission serum laboratory values were as follows: creatinine, 68 μ mol/L; urea nitrogen, 6.4 μ mol/L; hematocrit, 0.378; and glucose, 5.8 mmol/L. Following a blood transfusion, treatment was started with intravenous deferoxamine, 10 mg/kg per hour over 18 hours each day, and ascorbic acid, 500 mg orally per day. He tolerated the infusion well; however, overall, from day 5 to 10 his urine output was greater than his fluid intake. On the 10th day of intravenous deferoxamine his serum creatinine level was 101 μ mol/L (Fig 2); serum urea nitrogen, 6.2 mmol/L; hematocrit, 0.463; and weight, 55.4

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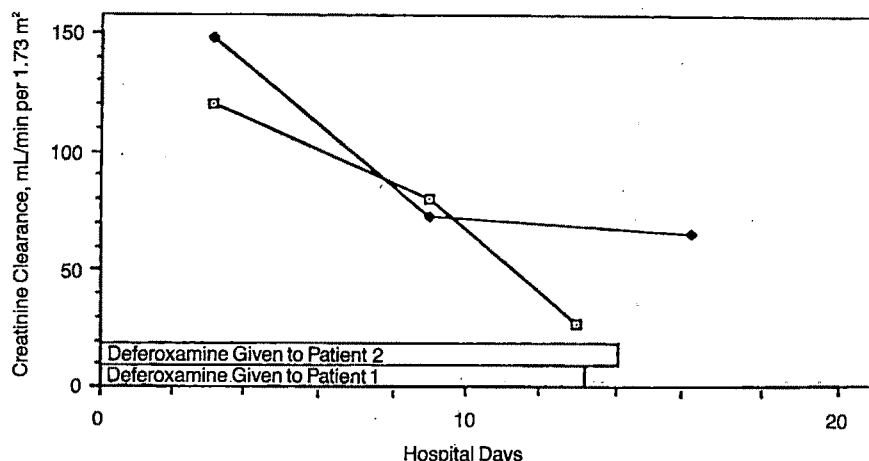


Fig 1.—Acute decrease in creatinine clearance in patients 1 (open squares) and 2 (solid diamonds) during intravenous deferoxamine therapy.

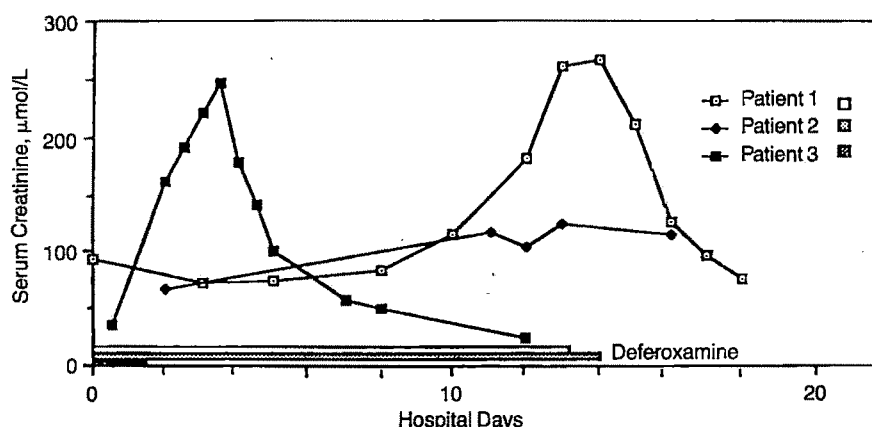


Fig 2.—Acute increases in serum creatinine level in patients during intravenous deferoxamine therapy, with subsequent improvement after discontinuation of the drug.

kg. Creatinine clearance continued decreasing throughout the infusion of deferoxamine (Fig 1). His blood pressure and heart rate remained unchanged. Deferoxamine therapy was discontinued on day 18, and he had the following serum laboratory values at discharge 2 days later: creatinine, 116 µmol/L; urea nitrogen, 7.9 mmol/L; and ferritin, 9146 µg/L. In a follow-up measurement 1 month later his serum creatinine level was 65 µmol/L.

PATIENT 3.—A 2-year-old white girl was admitted to the hospital for the treatment of accidental iron overdose 7 hours following ingestion of an unknown quantity of ferrous fumarate tablets belonging to her mother.

On physical examination the 10.7-kg girl had a heart rate of 120 beats per minute, a respiratory rate of 36/min, and a blood pressure of 86/60 mm Hg. She was lethargic, coughing, and vomiting and had black stools. She had the following serum laboratory values: ferritin, 284 µg/L; creatinine, 35 µmol/L; urea nitrogen, 10.2 mmol/L; glucose, 12.8 mmol/L; hematocrit, 0.409; and osmolality, 305 mmol/kg.

Fluids and deferoxamine (10 mg/kg per

hour) were administered intravenously. A day after deferoxamine chelation therapy was initiated, the child had very low urine output (30 mL for 24 hours) despite good hydration, blood pressure of 90/60 mm Hg, and heart rate of 100 beats per minute. Her serum creatinine level had increased to 191 µmol/L and serum urea nitrogen level to 17.5 mmol/L (Fig 2). Urinalysis revealed proteinuria (2⁺) and heme granular casts. Urine osmolality was 166 mmol/kg, and her sodium level was 60 mmol/L. Thirty hours after deferoxamine therapy began her serum iron level was 87 µmol/L, her hematocrit was 0.2820 without apparent bleeding, and her body weight was increased to 11.4 kg. Subsequently, deferoxamine therapy was discontinued; serum creatinine and urea nitrogen levels continued to rise for the next 24 hours and reached a maximum of 247 µmol/L (creatinine) and 18 mmol/L (urea nitrogen). An abdominal ultrasound at this time demonstrated a mild increase in kidney size with bilateral diffuse echogenicity, consistent with renal parenchymal injury.

Over the next 6 days her urine output increased, and her serum creatinine and urea

nitrogen levels declined (Fig 2). The serum creatinine level had returned to baseline at a clinic visit 2 weeks later.

ANIMAL STUDIES

Eight mongrel dogs that had free access to food and water prior to the experiments were premedicated with acepromazine maleate (1 mg/kg), anesthetized with pentobarbital (10 mg/kg), and mechanically ventilated. The external jugular veins, femoral artery, and both ureters were cannulated. An intravenous bolus of inulin (40 mg/kg) and para-aminohippuric acid (7 mg/kg) was followed by continuous infusion (inulin, 0.88 mg/kg per minute, and para-aminohippuric acid, 0.34 mg/kg per minute). After 40 minutes of equilibration at a saline infusion rate of 5 mL/kg per hour, 20-minute urine samples were collected with midinterval serum samples for calculation of inulin and para-aminohippuric acid clearances and for the determination of sodium, potassium, chloride, phosphate, and urate concentrations. Clearances were calculated as the ratio between the amount of a compound excreted in the urine in 1 minute and its midcollection plasma concentration. Fractional excretion was calculated as the ratio between the electrolyte clearance and that of inulin. After baseline measurements of clearance, deferoxamine (Desferal, Ciba-Geigy Corp, Summit, NJ) was infused at a rate of 10 mg/kg per hour for 2 hours. One hour after discontinuation of deferoxamine infusion, blood was drawn for deferoxamine determination, and the dogs were infused with saline at 40 mL/kg per hour to produce excessive diuresis (urine rate of 0.28 ± 0.086 mL/kg per minute); subsequently, deferoxamine infusion was restarted at the same dosage schedule for another 2 hours. Measurements of inulin and para-aminohippuric acid clearance and the various anions and cations were repeated at the various steps of the experiment (Fig 3). Arterial blood pressure was continuously measured by a manometer attached to an indwelling catheter at the left femoral artery. Infusion of all fluids was controlled by infusion pumps.

In another set of experiments, ferrioxamine solution was prepared by adding deferoxamine in the amount equivalent to infusion of 10 mg/kg per hour for 2 hours to 55 mg of iron dextran (Imferon, Fisons Corp, Bedford, Mass). The amount of iron was calculated to be twice the amount expected to be chelated by deferoxamine (100 mg of deferoxamine for 8.5 mg of iron¹). This solution was infused at a rate equivalent to 10 mg/kg per hour of deferoxamine to three additional dogs. The experimental protocol was identical to that described above, except for the volume expansion phase, which was not repeated.

Inulin clearance was measured by the

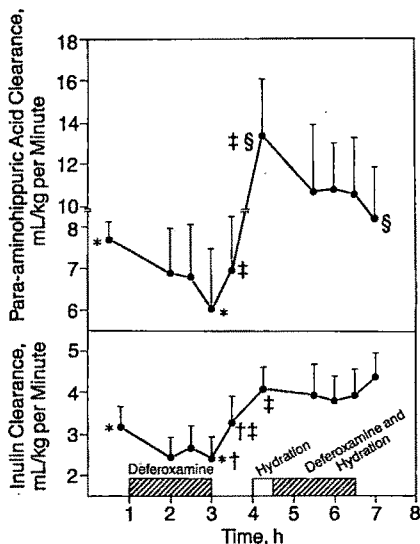


Fig 3.—Changes in inulin and para-aminohippuric acid clearances in dogs treated with deferoxamine, 10 mg/kg per hour, with or without saline diuresis. Asterisk indicates $P < .025$ for the baseline value compared with the value at the end of deferoxamine infusion; dagger, $P < .025$ for the value at the end of deferoxamine infusion compared with the value one half hour after the end of deferoxamine infusion; double dagger, $P < .050$ for the value one half hour after the end of deferoxamine infusion compared with the value 15 minutes after hydration was begun; and section mark, $P < .005$ for the value 15 minutes after hydration was begun compared with the value one half hour after deferoxamine infusion and hydration were stopped.

method described by Schreiner⁴ and para-aminohippuric acid clearance was measured by the method of Smith et al.⁵

Serum concentrations of deferoxamine were measured by a new high-pressure liquid chromatography method developed in our laboratory.⁶ Briefly, the procedure involves the use of ciprofloxacin as an internal standard followed by ultrafiltration to remove protein. The ultrafiltrate is then directly injected into the chromatography system. Separation is achieved using a reverse-phase C18 column and a ternary solvent system running at 2 mL/min. The lowest limit of sensitivity is 0.2 mg/L, and the coefficient of variation within day is 4.5%. Data in different treatment periods were compared by paired Student's *t* test or analysis of variance whenever applicable. At the conclusion of each experiment, kidneys were removed and inspected by gross examination, and tissue sections were processed. The sections were stained with hematoxylin-eosin, phloxin and saffron, periodic acid-Schiff, and Masson trichrome.

RESULTS

There was a significant decrease in inulin and para-aminohippuric acid

Fractional Excretion Values Induced by Deferoxamine					
	Fractional Excretion (Mean \pm SD)				
	Sodium	Potassium	Chloride	Phosphate	Urate
Normovolemia					
Before deferoxamine	0.44 \pm 0.14	18.5 \pm 3.4	0.32 \pm 0.13	10.6 \pm 0.8	14 \pm 0.86
End of deferoxamine infusion*	1.5 \pm 0.3	23.5 \pm 3.9	0.8 \pm 0.13	22.3 \pm 5.4	28.1 \pm 7.6
1 h after deferoxamine infusion†	0.85 \pm 0.19	17.9 \pm 0.8	0.46 \pm 0.18	9.8 \pm 2.5	22.2 \pm 3.16
Volume expansion					
Before deferoxamine	6.95 \pm 0.05	35.8 \pm 5.6	8.6 \pm 0.9	45.8 \pm 3.7	44.4 \pm 2
End of deferoxamine infusion*	17.6 \pm 0.2	42.2 \pm 6.9	19 \pm 1	66 \pm 5.4	60 \pm 22.7
1 h after deferoxamine infusion	15.1 \pm 4	32.6 \pm 0.6	16.4 \pm 4.1	51 \pm 3.1	41.8 \pm 10.5
Before ferrioxamine	0.34 \pm 0.15	16.93 \pm 4.41
End of ferrioxamine infusion	1.38 \pm 0.69	21.1 \pm 3.94
1 h after ferrioxamine infusion	1.8 \pm 0.80	22.53 \pm 3.04

*All values were significantly higher at the end of the deferoxamine infusion compared with before deferoxamine ($P < .05$ by analysis of variance).

†All values were significantly higher before deferoxamine after the initiation of saline infusion compared with values before saline infusion ($P < .05$ by analysis of variance).

clearances when deferoxamine was infused at the normovolemic phase ($P < .025$, Fig 3). No changes in arterial blood pressure were noted before and after deferoxamine infusion (115 \pm 13 and 118 \pm 13 mm Hg, respectively). Following discontinuation of deferoxamine infusion, both clearances returned to their baseline values, and serum deferoxamine concentrations were undetectable. The volume expansion resulted, as expected, in a significant increase in inulin and para-aminohippuric acid clearances as well as an increase in the urine flow rate (from 0.0125 \pm 0.0014 mL/kg per minute to 0.285 \pm 0.086 mL/kg per minute, $P < .001$). After volume expansion, deferoxamine did not cause a significant decrease in inulin clearance, whereas para-aminohippuric acid clearance decreased significantly ($P < .005$). Deferoxamine induced a rapid and significant increase in the fractional excretion of sodium, potassium, chloride, phosphate, and urate ($P < .05$) when tested both in the normovolemic phase and during volume expansion. These values returned to their baseline levels after discontinuation of deferoxamine infusion in the normovolemic phase and decreased, although not to baseline levels, in animals that had undergone volume expansion (Table). Deferoxamine serum concentrations were undetectable. Ferrioxamine did not cause any significant change in

para-aminohippuric acid clearance (6.04 \pm 1.73 mL/min per kilogram before ferrioxamine infusion and 6.16 \pm 0.64 mL/min per kilogram at the end of ferrioxamine infusion) or inulin clearance (2.40 \pm 0.43 mL/min per kilogram before ferrioxamine infusion and 2.47 \pm 0.34 mL/min per kilogram at the end of ferrioxamine infusion). Ferrioxamine induced an increase in the fractional excretions of sodium (fourfold) and chloride (fivefold) in all three animal studies (Table). These values did not return to baseline levels after ferrioxamine infusion was stopped; in fact, they continued to increase. No changes in arterial blood pressure were observed.

The capsular surface of the kidney appeared dark blue, consistent with congestion. By light microscopy, there was dilatation and congestion of peritubular capillaries, interstitial blood vessels, and glomerular capillaries; however, no other abnormalities of renal structure were seen, and the tubule appeared normal.

COMMENT

The interpretation of the three cases presented herein is complicated. There is no consistent history pattern (age difference, acute vs chronic intoxication; short-term vs long-term treatment; and their clinical course was different (abrupt vs gradual increase in serum creatinine concentration). In addition

it is impossible to rule out the effects of iron on renal function.

Although these cases do not form a homogeneous group, deferoxamine may have played a role in the development of acute renal failure. A controlled animal model seemed to be the proper way to study the potential nephrotoxicity of deferoxamine.

The animals were treated with a similar dosage schedule used clinically for treatment of iron overload in the three patients. Studies from our laboratory reveal that serum concentrations of deferoxamine in patients and dogs receiving the same dosage were comparable (between 3 and 12 g/L).^{7,8} We tested the potential renal effect of deferoxamine during normovolemia and after volume expansion in the dogs.

Our animal study demonstrated acute decreases in the glomerular filtration rate and renal blood flow induced by deferoxamine, without changes in systemic blood pressure. Because the hematocrit was not changed before and during deferoxamine infusion, changes in para-aminohippuric acid clearance reflect alterations in renal blood flow. These renal hemodynamic changes were reversed after deferoxamine infusion was discontinued. During volume expansion we were able to prevent the decrease in the glomerular filtration rate. We also demonstrated deferoxamine-induced increases in fractional excretion of sodium, potassium, chloride, phosphate, and urate in both the normovolemic and volume expansion phases; these were partially reversed by discontinuing deferoxamine infusion. The absence of morphologic changes under light microscopy supports the hypothesis of functional impairment.

Two mechanisms may explain deferoxamine nephrotoxicity:

1. There may be an acute decrease in renal perfusion in the presence of unchanged systemic blood pressure. That volume expansion prevented the decrease in the glomerular filtration rate may suggest a similarity to some of the renal effects of nonsteroidal anti-inflammatory drugs.^{9,10} Renal hemodynamics during borderline hydration or dehydration are significantly dependent on vasodilating prostaglandins. Furthermore, anesthesia can also increase the renal prostaglandin output with activation of the renin angiotension system.

The inhibition of prostaglandin synthesis, as in the case of nonsteroidal anti-inflammatory drugs, may be detrimental. It is still to be determined if deferoxamine affects prostaglandins; however, a recent report¹¹ supports this proposition.

2. Inhibition of tubular reabsorption of salts may take place, causing solute diuresis. Of interest are the findings that ferrioxamine induced an increase in the fractional excretion of sodium and chloride but did not cause any change in the glomerular filtration rate and renal blood flow. This ferrioxamine-induced tubular injury may suggest dissociation between the two observed effects of deferoxamine; that is, deferoxamine induced the renal hemodynamic changes whereas its iron chelate, ferrioxamine, caused the increased solute excretion. A synergistic effect between deferoxamine and ferrioxamine may exist as well, and further studies are needed.

Acute renal failure associated with deferoxamine therapy has been reported in a few cases^{12,13}; however, no attempt was made to prove causation, and a prerenal mechanism has been postulated. The high intravenous dose of deferoxamine used in patients 1 and 2 is much higher than the routine nightly subcutaneous infusion of the drug, suggesting a dose-related phenomenon. This suggestion is supported by Batey et al,¹¹ who found that increases in serum creatinine occurred only with the higher doses of deferoxamine (3 g/d for 2 days).

Our finding of increased solute excretion in the animal model may explain the relative diuresis seen in the two older patients with chronic iron overload and long-term deferoxamine treatment (possibly associated with higher ferrioxamine levels). This diuresis may have eventually caused volume contraction and prerenal azotemia. The toddler treated for acute iron intoxication presented with acute tubular necrosis, which may be explained by acute renal hemodynamic changes, as evidenced in the animal model. It is possible that both mechanisms had a role in the development of the acute renal failure in our patients; however, one cannot exclude one mechanism in the acute case and the other mechanism in the chronic case. In the past, renal damage seen during acute iron overdose was explained

mainly by the acute hemodynamic changes and possibly by a yet-unproved direct deposition of iron in the kidney. Our studies indicate that high-dose deferoxamine may be an important factor in affecting renal function during acute overdose.

To our knowledge, this is the first experimental proof of deferoxamine nephrotoxicity. Although more studies are needed to elucidate the mechanisms underlying this phenomenon, adequate hydration and repeated measurements of renal function should accompany intravenous deferoxamine therapy to prevent and detect possible renal failure.

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Dr Bentur is a fellow of The Hospital for Sick Children Foundation, Toronto, Canada.

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Methylphenidate in Children With Seizures and Attention-Deficit Disorder

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• This study assessed the safety and efficacy of methylphenidate in children with seizures and attention-deficit disorder. Ten children, aged 6 years 10 months to 10 years 10 months, without seizures while receiving a single antiepileptic drug, were evaluated in a double-blind medication-placebo crossover study with methylphenidate hydrochloride was administered at 0.3 mg/kg per dose and given at 8 AM and 12 PM on school days only. The use of methylphenidate was associated with statistically significant improvements on the Conners' Teacher Rating Scale and on the Finger Tapping Task and with trends toward improvement on the Matching Familiar Figures Test and Discriminant Reaction Time tests. No child had seizures during the study period nor subsequently for those who continued receiving psychostimulants. There were no significant changes of epileptiform features or background activity on electroencephalograms and no alterations in antiepileptic drug levels. Methylphenidate may be a safe and effective treatment for certain children with seizures and concurrent attention-deficit disorder.

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One of the major treatment options for children with attention-deficit disorder (ADD) is pharmacologic intervention with methylphenidate hydrochloride, a psychostimulant effective in prolonging attention, decreasing impulsivity, quieting hyperactivity, and improving classroom behavior.¹⁻⁶ The use of methylphenidate in children with seizures, whether or not they receive anticonvulsant therapy, is actively dis-

couraged by CIBA Pharmaceutical Company, the manufacturer of methylphenidate (Ritalin). The package insert and the *Physicians' Desk Reference*⁶ state that

there is some clinical evidence that Ritalin may lower the convulsive threshold in patients with prior history of seizures, with prior EEG [electroencephalographic] abnormalities in the absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and Ritalin has not been established. In the presence of seizures, the drug should be discontinued.

Many physicians, heeding these warnings, eliminate the option of methylphenidate therapy for children with the dual diagnoses of seizures and ADD.

Objective evidence for methylphenidate as an analeptic is scanty. The manufacturer cites rare clinical case reports. Previously, however, before monitoring the serum levels of antiepileptic drugs (AEDs) was available routinely, psychostimulants, including methylphenidate, had been used routinely in patients with seizures to counteract the sedative side effects of the AEDs.^{7,8} Dextroamphetamine sulfate, a related psychostimulant, was used as an adjunct AED for absence seizures.^{9,10} A recent retrospective study reviewed a cohort of 23 children who had either seizures or epileptiform features on electroencephalograms (EEGs) plus ADD.¹¹ The addition of methylphenidate to an AED regimen neither increased the frequency of seizures nor produced seizures in those with abnormal EEGs.

The goal of our study was to evaluate systematically the safety and efficacy of methylphenidate therapy for children with seizures and concurrent ADD, using a carefully controlled, "blinded" study design. We hypothesized, based on clinical experience and pilot data,

that methylphenidate would be effective in this population, as measured by standard behavioral questionnaires, laboratory studies sensitive to drug effects, or both. More importantly, using three criteria for safety, we hypothesized that methylphenidate would be safe. The first criterion was that there would be no increase in seizure frequency. The second criterion was that EEGs would not show increases in epileptiform activity. Previous studies of nonepileptic children have used the EEG as a predictor or parameter of improvement during methylphenidate therapy¹²⁻¹⁴ but have focused on background disturbance, not epileptiform features. The final criterion was that AED levels would not change with the introduction of methylphenidate. Previous studies of patients receiving multiple AEDs and of adult volunteers have reported varying effects of methylphenidate on AED levels.^{7,8,15}

SUBJECTS AND METHODS

Subjects

Ten patients from the Division of Child Neurology or Child Development Unit, Children's Hospital of Pittsburgh (Pa) (eight boys and two girls) aged 6 years 10 months to 10 years 10 months served as subjects. Table 1, organized by AED, provides age, sex, seizure type, educational level, and classroom placement for each subject.

The diagnosis of epilepsy, classification of seizure type, and choice of AED were established by child neurologists. The conditions of all the children were well controlled, with no seizures for at least 3 months preceding the study, as documented by medical histories. All of the children were receiving a single AED, with levels documented in the therapeutic range at the outset of the study. Five subjects had partial complex seizures, two generalized tonic-clonic seizures, two generalized atonic seizures, and one partial elementary motor seizure with secondary generalization. The AEDs included carbamazepine,

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Table 1.—Patient Characteristics

Patient No.	Sex/Age, y	Antiepileptic Drug	Seizure Type	Previous Stimulant Use	Grade	Class*
1	M/6.10	Carbamazepine	Partial complex	No	1-2	BD
2	M/10.6	Carbamazepine	Partial complex	Pemoline	5	LD
3	M/8.3	Carbamazepine	Partial complex	No	2	Mainstream
4	M/10.9	Carbamazepine	Partial complex	Methylphenidate hydrochloride	5	Mainstream
5	M/10.10	Carbamazepine	Generalized tonicoclonic	Methylphenidate	4	SED
6	M/6.11	Phenytoin sodium	Generalized atonic	No	2	Mixed MR/SED
7	F/7.5	Phenobarbital sodium	Generalized tonicoclonic	No	2	LD
8	M/8.0	Phenobarbital	Partial motor with secondary generalization	No	2	Mainstream
9	M/9.4	Valproic acid	Partial complex	Methylphenidate	4	LD/MR
10	F/8.1	Valproic acid	Generalized atonic	No	2	Mainstream

*BD indicates brain damaged; MR/SED, mixed category for mentally retarded and socially and emotionally disturbed; and LD, learning disabled.

phenobarbital, phenytoin, and valproic acid, with the largest subpopulation receiving carbamazepine ($n=5$). The parents of the two children receiving phenobarbital reported that attention problems or hyperactivity began before the use of phenobarbital and that the symptoms did not change with use of a different AED or reintroduction of phenobarbital therapy.

Children were identified for enrollment because of parental or school concerns of inattention or overactivity. The diagnosis of ADD with or without hyperactivity was established in a clinical interview with a parent(s) by a developmental pediatrician using criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*¹⁶ and confirmed with the Revised Conners' Parent and Teacher Behavior Rating scales.¹⁷ On these scales, behavior characteristics are rated on a four-point scale from "not at all" to "very much." Ten items on each scale form the Hyperactivity Index. Raw scores on the Hyperactivity Index were converted to age- and sex-normed z scores.¹⁷ Each child scored 1.5 SDs or more above the mean for age and sex on this scale. Three children were receiving psychostimulants at the time of recruitment but had not had systematic monitoring of seizure frequency, AED levels, or EEGs while receiving methylphenidate. These children were given a 2-week drug-free period before beginning the study, after which the baseline questionnaires were obtained. One subject had been receiving methylphenidate a year before the study. Children were not excluded on the basis of IQ. The protocol was approved by the Children's Hospital of Pittsburgh Institutional Review Board. Written informed consent from parents and verbal assent from children were obtained at the first visit.

Study Design

The study used a double-blind methylphenidate-placebo crossover design, with each subject serving as his or her own control. Methylphenidate hydrochloride was administered at 0.3 mg/kg per dose, rounded up to the nearest 2.5 mg, and was given twice a day, at 8 AM and 12 PM, on school days only. The lower end of the dosing range was selected to minimize the risk of seizures. The trials of methylphenidate-placebo lasted 4 weeks. There was a 2-week washout between trial periods because of the possible long-lasting effects of methylphenidate on the EEGs.¹⁸

Parents were instructed to call the study team if seizures occurred. Children were evaluated at baseline and at the midpoint and end of the 4-week trials. Each session was at the same time of day to avoid circadian fluctuations in AEDs. Psychological testing began 30 to 45 minutes after methylphenidate administration, and EEGs and serum AED levels were obtained about 2 hours after methylphenidate was administered—at its presumed peak level. At each visit, the parents were interviewed about clinical improvements, seizure activity, the toxic side effects of AEDs, and the side effects of methylphenidate. One child did not complete the placebo trial because his parents and teachers became very concerned about his increased activity and disruptiveness. We used baseline data for his placebo phase in the analyses of rating scales and laboratory testing.

Rating Scales

Teachers were asked to complete the 28-item Revised Conners' Teacher Rating Scale¹⁷ midway and at the end of each trial.

The individual items were grouped into four established factors, conduct problems, hyperactivity, inattention-passivity, and the hyperactivity index, as described by Goyette et al.¹⁷ The factor scores were used for data analysis. For most children, two questionnaires were given in each study trial, and the scores were averaged.

Parents were asked to complete the 48-item Revised Conners' Parent Rating Scale.¹⁷ The scores were handled analogously to the Teacher's Rating Scale. No changes were noted on the Parent Rating Scale, and the scores are not reported in this article.

Laboratory Tests

Children were tested at baseline to introduce them to the procedures and at the end of each trial. One child could not complete the battery because of intellectual limitations, learning problems, or both; the data for the laboratory tests comes from nine subjects.

A Discriminant Reaction Time Test, a computerized test of selective attention, was administered using a revision of the Lewis and Rennie¹⁹ Repeatable Cognitive-Perceptual-Motor Battery. The test involved the rapid presentation of numbers on a screen and required the child to depress a computer key at the appearance of a preselected target stimulus. Children could make errors of omission and commission. The rate of stimulus presentation increased by 5% after a correct response and decreased by 5% after an incorrect response or omission. The score reported was the final number of stimuli presented per minute; the higher the score, the greater the speed, accuracy, or both.

The Matching Familiar Figures Test,²⁰ a measure of reflectivity or impulsivity, required the child to identify which of six figures matched a simultaneously presented target stimulus. The procedure was modified such that the child made only a single response without feedback rather than responding until successful. This modification eliminated the possibility that the child would remember the correct response on later test administrations. The score on this test was the latency of response in seconds.

A Finger Tapping Task, a measurement of neuromotor output, was administered to assess the influence of attentional skills on neuromotor efficiency. The child tapped a Reitan finger counter mounted on a board, with separate trials for the dominant and nondominant hand. The score for each hand was the mean number of finger taps over five 10-second trials.

The Digit Span from the Wechsler Intelligence Scale for Children-revised, a measure of attention and immediate memory, required the child to repeat a random string of digits of increasing length. The method of administration followed the test protocol.²¹

Raw scores were converted to age-normed standard scores, with a mean of 10 and an SD of 3.

A spelling learning test and mathematics performance test were piloted. However, because of difficulty in establishing appropriate baseline levels of success across subjects, no consistent trends were noted, and the results are not reported.

EEG Findings

The EEGs were obtained before each trial (baseline 1 and 2) and at the end of each study trial for a total of four studies per child (except for the child who dropped out in the placebo trial). A 30- to 45-minute standard 16-channel EEG using the international 10-20 electrode placement was obtained approximately 2 hours after methylphenidate administration. Attempts were made to record brain waves during awake and sleep states.

The EEGs were read by a child neurologist experienced in pediatric EEG. The EEGs were assigned random numbers and interpreted blindly relative to the subject and study trial. Background abnormalities were defined as increased slower frequencies posteriorly relative to chronological age without sustained rhythmicity. Epileptiform features were defined as focal or generalized sharp waves, spikes, or spike and wave complexes. The EEGs were classified as normal, abnormal with background disturbance, abnormal with epileptiform features, or abnormal with both background disturbance and epileptiform features. A second review was completed with the EEGs organized sequentially by subject with the reviewer blinded to the study phase. On this review, the EEGs were analyzed for the severity of the abnormalities.

AED Levels

Serum AED levels were obtained at baseline and twice during each trial at the end of the week. All AED levels were obtained approximately 2 hours after methylphenidate administration. Specimens were analyzed in the same laboratory using a fluorescent polarization immunoassay. Values at baseline and within the methylphenidate and placebo trials were averaged separately for data analysis.

Final Interview

Five children continued receiving psychostimulants (four received methylphenidate and one received pemoline) for 3 to 12 months after the study period based on clinical efficacy and parental preference. During the preparation of this report, the parents of these children were recontacted by telephone. They were questioned about further seizures and drug side effects.

Table 2.—Mean Scores on Factors of Conners' Teacher Rating Scales During Placebo and Methylphenidate Trials

Factors	Placebo	Methylphenidate Hydrochloride	No. of Children Improving While Receiving Methylphenidate
Conduct	7.85 ± 7.53	5.60 ± 5.35	6
Hyperactivity	10.75 ± 5.51	6.65 ± 3.97*	7
Inattention	10.60 ± 4.70	7.40 ± 3.66*	6
Hyperactivity index	15.25 ± 7.73	9.20 ± 5.91*	7

* $P < .05$.

Table 3.—Mean Scores on Laboratory Tests During Placebo and Methylphenidate Trials

Test	Placebo	Methylphenidate Hydrochloride	No. of Children Improving While Receiving Methylphenidate
Discriminant Reaction Time	23.91 ± 9.69	26.41 ± 11.05	5
Matching Familiar Figures			
Test Latency, s	8.20 ± 9.60	10.96 ± 8.51	8
Finger tapping			
No. of taps, dominant hand	32.23 ± 7.00	35.24 ± 7.96*	7
No. of taps, nondominant hand	28.33 ± 11.51	29.62 ± 10.73*	6
Digit Span			
standard score	8.3 ± 3.43	8.0 ± 3.40	4

* $P < .05$.

Data Analysis

A one-way repeated-measures analysis of variance was used to analyze subscales of the Conners' Teacher Rating scales, scores on the psychological tests, and AED levels for order effects. Order effects were not statistically significant, and the conditions were analyzed independent of order. A one-tailed paired t test compared the same scores in the placebo and methylphenidate phases.

RESULTS

Table 2 shows the average scores for the four factors of the Conners' Teacher Rating Scale. All four factors showed reductions during the methylphenidate trial, and the decreases on three of the factors reached statistical significance (hyperactivity: $t = 2.672$, $df = 9$, $P < .05$; inattention: $t = 2.154$, $df = 9$, $P < .05$; and Hyperactivity Index: $t = 2.457$, $df = 9$, $P < .05$).

The magnitude of the improvement during the methylphenidate trial was quantified by converting raw scores to age- and sex-normed z scores. On the Hyperactivity Index of the Conners' Teacher Behavior Rating Scale,¹⁷ the group averaged a 1.0-SD improvement, with a range from -1.31 to $+3.08$ SDs.

In the seven responders, the average improvement was 1.6 SDs.

Table 3 shows the results of the laboratory testing. There were significant improvements in the Finger Tapping Task with both the dominant hand ($t = 6.167$, $df = 8$, $P < .05$) and the nondominant hand ($t = 6.526$, $df = 8$, $P < .05$). On the Matching Familiar Figures Test, eight of nine children showed longer latencies while receiving methylphenidate, but the latency score did not achieve statistical significance ($t = 1.238$, $df = 8$). Performance on the Discriminant Reaction Time Test also showed a trend toward improvement using methylphenidate, with five children increasing their score ($t = 1.341$, $df = 8$, not significant). There was no systematic change in findings from the Digit Span.

None of the children had seizures during the study period according to the parents and teachers. Of the five children who continued receiving psychostimulants beyond the study period, none had seizures during the extended period. There were no dose-related toxic side effects of AEDs, such as visual disturbances, coordination problems, or

Table 4.—Electroencephalographic Results During Placebo and Methylphenidate Trials

	Baseline 1 (n = 10)	Baseline 2 (n = 10)	Placebo (n = 9)	Methylphenidate Hydrochloride (n = 10)
Normal	1	1	1	2
Abnormal	9	9	8	8
Background disturbance	2	2	2	2
Epileptiform features	3	3	2	2
Both	4	4	4	4

Table 5.—Average Antiepileptic Drug Levels for Individual Subjects at Baseline, Placebo, and Methylphenidate Trials

Antiepileptic Drug	Subject	Baseline	Placebo	Methylphenidate Hydrochloride
Carbamazepine, mg/dL	1	7.70	6.80	7.85
	2	8.60	8.65	8.10
	3	5.80	8.05	8.95
	4	8.15	9.60	7.60
	5	9.15	3.05	8.85
Phenytoin, mg/dL	6	11.40	12.15	9.45
Phenobarbital, mg/dL	7	24.75	25.50	26.05
	8	8.65	9.10	10.60
Valproic acid, mg/dL	9	75.30	—	90.80
	10	63.15	86.70	74.85

behavioral changes. Two parents reported mild side effects attributable to methylphenidate administration—appetite suppression and minor emotional lability. In both cases the effects were transient and did not alter drug treatment.

All but one patient had abnormal features on baseline EEG (Table 4). There were no significant changes from the first to second baseline or from baselines to study trials. The child with the normal EEG at baseline had normal EEGs throughout the clinical trials. No child with background abnormalities developed epileptiform features. One patient with epileptiform features at baseline had a normal EEG during the methylphenidate trial (Table 4).

Two patients with preexisting epileptiform features had minor changes during methylphenidate administration. One of these patients had prominent photoparoxysmal responses at baseline and during methylphenidate therapy but not during the placebo trial. Another patient had frequent bursts of generalized spike-wave complexes during the records of all trials but more frequent

bursts of 1- to 3-second duration during the methylphenidate trial (61.7 bursts per 60 minutes while receiving methylphenidate vs 29 at baseline and 40 while receiving placebo). No corresponding increases in the number of longer bursts lasting 3 to 5 seconds or greater than 5 seconds were noted. Although a video EEG was not obtained, there were no alterations in behavior or consciousness suggestive of seizures as observed by trained EEG technologists.

The AED levels fell in the subtherapeutic range on 5 of 58 determinations during the study. Twice there was poor compliance and once repeated vomiting on the day before determination. These 3 values were eliminated in further analyses because they were not relevant to the issue of drug interactions. On 2 determinations, once when methylphenidate was used and once when the placebo was given, a child whose dose of phenobarbital was maintained at the low end of the therapeutic range had levels in the subtherapeutic range. Average AED levels for each subject at baseline, methylphenidate, and placebo trials are presented in Table 5. The val-

ues are consistent across conditions. The mean level of carbamazepine for the five children receiving this AED was 8.09 during methylphenidate therapy and 8.41 during placebo therapy; these values were not significantly different ($t = 0.568$, $df = 4$).

COMMENT

The prevalence of the concurrent diagnoses of seizures and ADD is difficult to ascertain due to significant differences in definitions across studies. Ounsted,²² in an early study of epileptic children, reported that "hyperkinetic syndrome" was present in about 8% of cases, comparable with the 3% to 10% prevalence rate usually reported for ADD in nonepileptic American school children.²³ However, the descriptions of the disorder in that article²² and the associated mental retardation in 50% of the patients suggested that the term connoted extreme behavioral deviance. Prevalence rates might have been higher with the inclusion of milder variants of the syndrome. Rutter et al,²⁴ in their epidemiologic study from the Isle of Wight, reported that only 1 in 63 children with uncomplicated epilepsy had hyperkinetic syndrome, a lower rate than the usual American prevalence figures but comparable with estimates of ADD in school-aged nonepileptic British children.²⁵ These authors, however, found that 28% to 50% of children had symptoms of restlessness, fidgetiness, and poor concentration on parent and teacher questionnaires. Prevalence rates might have been higher using criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* for ADD.

In the clinical practice of developmental pediatrics and child neurology, the problem of concurrent seizures and ADD is encountered regularly. The strong warning about methylphenidate treatment in children with seizures with abnormal EEGs who are receiving AEDs⁶ thrusts the clinician into a dilemma regarding treatment options. Many physicians do not consider prescribing methylphenidate to children with seizures because of medicolegal concerns. Frequently, there are additional intellectual and learning problems in these children,^{22,24} further complicating clinical decision making because of the lack

of articles on the use of methylphenidate in nonhospitalized mentally retarded children. In this sample, 60% of the children were in special educational programs.

The data from this study suggest that methylphenidate therapy may be an option for certain children with seizures and concurrent ADD. We were able to demonstrate that methylphenidate was efficacious in children with seizures. As in many other studies, questionnaire data provided by teachers was the most consistent indicator of the effect of methylphenidate therapy. Seven of 10 children improved on the Teacher's Behavior Rating Scale, a response rate comparable with that in many other studies.⁵ In this study, the failure of the Parent Rating Scale to show improvements during methylphenidate therapy was not surprising, since the half-life is 4 to 6 hours and we used a schedule of administering doses on school days only so that parents had minimal experience with their children at peak methylphenidate effects. Laboratory tests also confirmed the efficacy of methylphenidate therapy. The children were more efficient on the Finger Tapping Test while receiving methylphenidate. They seemed to use a more reflective, less impulsive approach on the Matching Familiar Figures Test and to improve selective attention on the Discriminant Reaction Time Test. In this intellectually heterogeneous sample, however, these two latter tests failed to achieve statistical significance because of extreme variability on performance.

The data suggest that methylphenidate may be used safely in children who have seizures that are well controlled on an AED regimen. No child had a clinical seizure during the study period or during subsequent use. The AED levels remained stable. Even in those five patients whose AED levels dropped to the

subtherapeutic range, there were no reported seizures. Patterns of epileptiform activity and background disturbance on an EEG did not systematically deteriorate during methylphenidate therapy. If seizure recurrence with methylphenidate is a rare complication, then a large sample would be required to demonstrate the risk. However, in this situation, the warning in the *Physicians' Desk Reference* could be modified.

The warning about methylphenidate use in children with abnormal EEGs is particularly confusing given the significant number of children with ADD and abnormal EEGs.²⁶⁻²⁸ In our cohort, 90% of subjects had abnormal EEGs, with 70% showing epileptiform features either alone or in combination with background slowing. Klinkerfuss et al²⁷ reported that 53% of their subjects with hyperkinesia and other neurologic problems, including seizures, had abnormalities on their EEGs.

No major changes in epileptiform features on the EEGs were associated with methylphenidate administration. The significance of epileptiform features on an interictal EEG is unclear. Epileptiform features are more likely to be present in subjects with a history of epilepsy than in the general population,²⁹ but whether increases in the number of epileptiform features correlate with changes in seizure frequency is not well documented. There are clearly many other variables associated with variations in epileptiform features, such as a change in state from wake to sleep and the use of drugs. In our sample, one child had changes in the frequency of one type of epileptiform activity but had no changes in clinical seizure pattern. A review of this child's EEGs before the study demonstrated that EEG patterns at earlier times were similar to the EEGs during methylphenidate therapy.

Therefore, we cannot relate the change only to methylphenidate administration. Sampling artifact remains a possibility for all the observed changes.

Despite these findings, continued caution in prescribing methylphenidate for children with seizures and ADD is warranted. First, all of the children in this study had well-controlled seizures with a seizure-free interval before enrollment. McBride et al,¹¹ however, noted that none of their patients who were having seizures at the time methylphenidate therapy was introduced had increases in seizure frequency. Second, the time course of the study was relatively short. However, the children who continued to use psychostimulants beyond the study period remained seizure free. Finally, our dosages of methylphenidate were at the low end of the effective range.

Our clinical experience has been that many physicians violate the warning and recommendations in the *Physicians' Desk Reference*.⁶ As with the use of methylphenidate for children with uncomplicated ADD, the use of methylphenidate in children with seizures and ADD should follow a careful diagnosis of ADD, clear demonstrations of clinical efficacy, and close monitoring of behavioral and neurologic complications. The use of methylphenidate should be integrated with other educational and behavioral treatments.

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ARCHIVES OF INTERNAL MEDICINE

Evaluation of the Do Not Resuscitate Orders at a Community Hospital

Cynthia J. Stolman, PhD; John J. Gregory, MD; Dorothea Dunn, RN, MS; Barbara Ripley, LPN (*Arch Intern Med*. 1989;46:1851-1856)

Complete Heart Block as the Sole Presentation of Lyme Disease

Suzanne A. Kimball, DO; Paul A. Janson, MD; Paul J. LaRaia, MD (*Arch Intern Med*. 1989;46:1897-1898)

Attitudes Toward Mental Illness Prevention in Routine Pediatric Practice

Joel Yager, MD; Lawrence S. Linn, PhD; Barbara Leake, PhD;
Stephen Goldston, EdD; Christoph Heinicke, PhD; Robert Pynoos, MD

• Attitudes toward preventive mental health activities with high-risk children in clinical practice were surveyed in 316 pediatricians. Although generally positive attitudes were expressed regarding appropriateness and efficacy of such activities, uncertainty was expressed regarding the ethical issues and knowledge on which such activities rest. Pediatricians perceived serious barriers to preventive activities related to financial, educational, and time factors. Pediatricians whose personal health beliefs favored an internal locus of control were more positively inclined toward preventive activities. Studies relating reported attitudes and beliefs to actual practice patterns are necessary. Pediatricians also require additional training in mental health-related preventive activities.

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The prevention of illness and injury has traditionally played a major role in primary care pediatric practice. Although many of these practices relate to physical well-being,^{1,2} psychological and social aspects such as child abuse and learning disabilities also receive attention.³

The pediatrician is often the first health professional to identify opportunities for mental illness prevention. Yet, many opportunities for prevention are undoubtedly overlooked. For example, children of parents who are divorced, depressed, or hospitalized with major mental illnesses constitute major patient groups for prevention.⁴

Prevention efforts with these and other potential "high-risk" groups represent a departure from traditional pediatric practice. To our knowledge there are no previous studies regarding pediatricians' attitudes about what should constitute their proper roles in such situations. Therefore, we surveyed the attitudes of pediatric house staff, fellows, and academic and clinical (volunteer) faculty toward the appropriateness and efficacy of such mental illness prevention with high-risk children in their clinical work. In addition to developing reliable and valid scales to measure these attitudes, we hoped to identify perceived barriers to the initiation of preventive programs or activities in clinical situations.

We were also interested in identifying factors that may be significantly correlated with attitudes toward prevention such as pediatricians' age, sex, level of training or type of practice, earlier pre-medical school work experiences, career plans, and selected general beliefs about how people stay healthy. Studying the relationship between these factors and attitudes toward prevention may help researchers and educators develop a better understanding of how pediatricians develop different orientations toward prevention in clinical practice.

METHODS Design and Samples

The present study surveyed all PLI-III pediatric residents and those full-time academic faculty and clinical faculty actively involved with house staff supervision in the UCLA Department of Pediatrics affiliated with the UCLA Center for Health Sciences during the spring of 1987. Questionnaire items were modified from scales previously developed in a parallel study of psychiatrists'

attitudes toward prevention that had been validated using samples of physicians on the editorial boards of the *Journal of Preventive Psychiatry* and the *Journal of Primary Prevention* (N = 29).⁵

After two mailings, 316 of the questionnaires initially mailed were returned, constituting a 70% response rate. The percentages of the total sample of respondents consisted of the following groups: 16% house staff, 67% community-based clinical (volunteer) faculty, and 17% full-time academic faculty. The median age of the sample was 45 years; 26% were women; 90% were currently married; 92% were white; and 20% were Catholic, 20% were Protestant, 49% were Jewish, 11% had no expressed religion, and 1% had a religious affiliation that did not fall within our classification.

Measurements

Items measuring attitudes toward mental illness prevention were generated from the content of a training grant proposal in clinical preventive intervention written by several department faculty members and from an article on prevention written by Phillips.⁴ Specific modifications of items for pediatricians were written in consultation with members of Valencia Pediatric Associates, Newhall, Calif, a private practice group whose members are all active on the UCLA volunteer faculty. Equal numbers of positively and negatively worded items were written to avoid response bias, and respondents were asked to rate each item on a five-point scale from strongly agree to strongly disagree. Items were written to reflect three dimensions of attitudes toward mental health-oriented prevention in routine pediatric practice: role appropriateness for interventions with high-risk children, perceived efficacy, and perceived ethics of such interventions. Other items measured attitudes toward barriers potentially related to initiating preventive mental health measures such as insufficient time, financial constraints, inadequate knowledge or training, and patient resistance. These were not the only barriers that

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could restrict preventive mental health activity in clinical practice but represented those thought to be most likely by our faculty group.

Physicians' health beliefs were measured by three health locus of control scales developed by Lau and Ware⁶: (1) the degree to which luck or chance influenced peoples' health status, (2) the degree to which people generally felt threatened by serious diseases, and (3) the degree to which people felt they could control their own health through self-care or preventive health behaviors. These scales were scored in such a way that higher scores indicated greater internal or self-control over health (and thus were less influenced by external forces such as serious disease or chance).

In addition to demographic characteristics such as age, sex, marital status, race, and religious affiliation, the pediatricians answered questions about the number of social sciences and humanities courses they took in college, whether they held an advanced degree other than the MD, how many vacation days they had taken in the past 12 months, how many hours a week they worked, how many research or clinical journals they read on a regular basis, and how many scholarly articles they had published in their careers. Respondents were also asked to estimate the likelihood of their pursuing eight career options on a scale of 0% to 100%.

Hypotheses

The following null hypotheses were tested: that there is no significant relationship between pediatricians' attitudes toward mental illness prevention and their demographic and social characteristics, health beliefs, educational background, or previous scholarly activity.

RESULTS

Scale Construction

Principal components factor analysis was used to test our conceptual model of attitudes regarding preventive mental health treatment. After inspection of factors with eigenvalues greater than 1.0, we decided to limit further analysis to eight factors. Varimax rotation was used to obtain meaningful factor constructs. Items were only included in scales if they had a loading greater than 0.49 on a factor with an eigenvalue greater than 2.0. Based on this analysis, Table 1 shows that we were able to construct five modestly reliable scales reflecting the dimensions of attitudes toward prevention and barriers that might inhibit such clinical activity.

Table 1.—Characteristics of Scales Developed to Measure Attitudes Toward Preventive Mental Health Activities in Routine Pediatric Clinical Practice

Scale	No. of Items	Average Item Score	SD	Range of Scores	Cronbach's α
Appropriateness*	6	4.15	0.45	2.67-5.0	.54
Efficacy*	11	3.55	0.52	1.82-4.73	.82
Ethics*	4	3.73	0.68	1.75-5.0	.60
Financial barriers†	2	2.05	0.82	1.0-5.0	.50
Education and time barriers†	3	2.61	0.82	1.0-5.0	.58

*Higher scores indicate more positive attitudes.

†Higher scores indicate that barriers are seen as more inhibiting.

Scale means were calculated based on the sum of the item scores (1 through 5) divided by the number of items in the scale. Higher scores on the appropriateness, effectiveness, and ethics scales indicated more positive attitudes. Higher scores on the two barrier scales (financial barriers and time and educational barriers) indicated greater belief in the barrier.

Illustrative items and responses from each of the five scales are presented in Table 2. Copies of the complete questionnaire, the 29 items making up the scales, and item-by-item responses are available on request from the senior author (J.Y.). Pediatricians almost always either strongly or somewhat agreed that preventive mental health-oriented interventions with high-risk children were appropriate. There was some uncertainty and almost no disagreement on most items. Generally two thirds or more of the sample felt that preventive measures were appropriate in the situations described (scale mean, 4.15).

Although generally favorable attitudes were expressed about the efficacy of prevention (scale mean, 3.55), there was considerable uncertainty and disagreement about whether the efficacy of prevention had been substantiated by research evidence.

As shown in Table 1, there was also favorable consensus in our sample that such preventive mental health measures were ethical (scale mean, 3.73). However, Table 1 also shows that there was strong consensus about two important barriers to preventive activities: financial issues (scale mean, 2.05) and time and educational barriers (scale mean, 2.61). Responses to items in

these scales indicated strong belief that neither patients nor third-party payers were willing or likely to pay for preventive mental health services. Similarly, there was general consensus that pediatricians lacked appropriate training to do prevention, and very divided opinion about whether pediatricians had sufficient time to be concerned about the mental health of their patients.

Some additional items measuring attitudes toward barriers did not form reliable scales. Responses to these items indicated that there was very divided opinion and much uncertainty regarding the pediatrician's role with the children of psychiatrically hospitalized parents. Similarly, pediatricians were divided in the degree to which they felt that preventive mental health practice entailed more uncertainty than other kinds of pediatric practice or whether mental health-oriented prevention was unlikely to become part of routine practice due to the usual orientation of physicians in which acute problems are the primary focus of concern. Finally, there was also disagreement regarding whether the organization of both residency training and private practice inhibited the initiation of preventive mental health-oriented practice.

In summary, our samples generally agreed that mental health-oriented prevention with high-risk children in routine clinical practice was very appropriate, ethical, and somewhat effective. They also generally believed that the lack of reimbursement for preventive services and the lack of adequate psychiatric training in prevention were significant barriers inhibiting the expansion of mental illness prevention.

Table 2.—Frequency Distributions of Illustrative Items From Five Scales Used to Measure Attitudes Toward Preventive Mental Health Activities in Routine Pediatric Clinical Practice

Items	% of Agreement				
	(5) Strongly Agree	(4) Somewhat Agree	(3) Uncertain	(2) Somewhat Disagree	(1) Strongly Disagree
Appropriateness					
It is the pediatrician's responsibility in treating a patient with serious illness to assess the extent to which the patient's family members have been affected psychologically.	64	34	1	2	0
Intervening in the lives of the children of a psychiatric patient constitutes high-quality pediatric practice.	36	43	15	5	1
Efficacy					
Preventive mental health interventions are generally worth the amount of time they take.	40	40	16	3	0
Preventive mental health sounds good as a concept, but in reality there is little evidence that preventive interventions are effective.	2	11	25	41	20
Ethics					
Attempting to intervene in the lives of the children of a psychiatric patient poses a serious ethical problem.	3	12	15	41	29
Preventive mental health efforts initiated by a pediatrician are potentially unethical because they are too intrusive.	1	1	7	37	54
Financial Barriers					
Most people at the present time are not very willing to pay for most preventive mental health interventions.	27	48	10	12	27
Third-party payers are not very likely to support reimbursement for preventive mental health interventions.	40	34	19	6	2
Educational/Time Barriers					
Pediatricians often find it difficult to initiate many preventive mental health measures because they are not trained to do so.	27	57	4	9	4
Pediatricians rarely have time to be concerned about the mental health of their patients.	5	27	9	40	19

Intercorrelations Among Scales and Barriers

Pearson correlation coefficients were calculated among the scales measuring attitudes toward prevention and barriers inhibiting preventive practice. All three attitudes toward prevention scales were positively correlated with each other ($P < .05$ to $P < .001$). Attitudes regarding financial barriers were negatively related to attitudes regarding the appropriateness of mental illness prevention ($P < .01$) but were unrelated to attitudes regarding the ethics or efficacy of mental illness prevention. That is, pediatricians who viewed mental illness prevention as less appropriate were more likely to feel that cost factors inhibited preventive mental health practice. Attitudes regarding educational and time barriers were positively related to attitudes regarding efficacy ($P < .02$), ethics ($P < .001$), and fi-

nancial barriers ($P < .001$). That is, pediatricians who perceived educational and time barriers as being more operative were also more likely to perceive financial barriers to mental illness prevention, but were also more likely to feel that such interventions were both effective and ethical.

Attitudes Toward Prevention and Pediatricians' Sociodemographic and Work Characteristics

Based on Pearson correlation coefficients and/or one-way analysis of variance, we found few relationships among scores on any of the five attitude and barrier scales with respondents' sex, race, religious affiliation, the amount or kind of course work they took before medical school, the number of hours they worked in an average week, or the number of journals they regularly read in an average month. Female pediatricians were slightly more likely than

male pediatricians to perceive mental illness interventions as appropriate ($\chi = 4.27 \pm 0.47$ vs 4.12 ± 0.44 ; 1 *df*; $F = 8.30$; $P < .004$). Academic pediatricians ($\chi = 3.35$) were less likely to perceive such interventions to be efficacious than house staff ($\chi = 3.55$) or clinical faculty ($\chi = 3.60$) (2 *df*; $F = 4.86$; $P < .008$).

Those pediatricians who had taken more humanities courses in college were more likely to perceive mental health-oriented prevention as role appropriate ($r = .154$; $P < .01$) and those reporting longer work weeks were a little less likely to see such interventions as efficacious ($r = -.147$; $P < .001$).

In looking at the relationship between career aspirations and attitudes toward prevention, only a few significant correlations were found. Pediatricians who were in or who aspired to careers in public health were a bit more likely to view mental health-oriented

prevention as role appropriate ($r = .154$; $P < .01$) and efficacious ($r = .133$; $P < .03$), and those who were in or aspired to a teaching affiliation were significantly more likely to feel that mental health-oriented prevention was appropriate ($r = .186$; $P < .001$). In contrast, pediatricians more likely to be in or aspire to a tenure track academic career felt that prevention was less efficacious ($r = .151$; $P < .01$).

Attitudes Toward Mental Health-Oriented Prevention and Personal Health Beliefs

Pediatricians answered 19 items constituting three scales that measured different dimensions of their beliefs about the locus of control in health matters: the role of chance, the general threat of serious disease, and the role of self-control and self-care. On these scales, higher scores indicated stronger beliefs in internal vs external factors (ie, a lesser role of chance and of serious disease as a threat to health and the greater importance of self-care).

In looking at the relationship between these health belief scale scores and our pediatricians' attitudes toward prevention, pediatricians who expressed more positive attitudes toward the efficacy of mental health-oriented prevention in their clinical practice were less likely to believe in the role of luck or chance in good health ($r = .22$; $P < .001$), less likely to view good health as seriously threatened by disease ($r = .15$; $P < .01$), and more likely to favor self-care ($r = .26$; $P < .001$). A favorable attitude toward the appropriateness of mental health-oriented prevention in clinical practice was also positively related to the importance of self-care ($r = .19$; $P < .001$).

COMMENT

Because our sample was drawn from a single medical school's pediatrics department, rather than from a broader community sample of practicing pediatricians, our response rate was only 70%, and the study relied entirely on self-report questionnaire measures, our results must be considered preliminary and may not be generalizable to all pediatricians. However, with these caveats

in mind, given that between 3% and 10% of patients under the age of 18 years are diagnosed in outpatient settings as having some type of mental disorder,⁷ it is encouraging that our sample of pediatricians expressed generally favorable attitudes toward the appropriateness, efficacy, and ethical nature of mental illness prevention in their practices. However, they also expressed significant uncertainty about the adequacy of the data on which the literature is based, and considerable concern that educational, financial, social, and organizational barriers had inhibited the growth of preventive mental health-oriented practices in pediatrics. Although we can be reassured that these pediatricians endorsed such prevention so favorably, additional studies of other groups of pediatricians are needed to determine the extent to which our preliminary findings can be generalized. The extent to which such positive attitudes are sufficient to actually overcome the numerous barriers that pediatricians also perceived is unknown. Studies relating the attitudes we studied to actual practice patterns are necessary to answer this question, especially since several recent studies conducted in primary medical care settings revealed that appropriate preventive care fell significantly short of generally agreed-on standards.⁸⁻¹⁰

Although many of the factors that we studied in relationship to attitudes toward mental illness prevention yielded weak, inconsistent, or no associations, several consistent trends in the findings are noteworthy. The significant associations between pediatricians' preventive practice orientations and their own personal health beliefs, previous interest in the humanities, and work habits suggest that prevention is one area in which personal beliefs may affect the practice behaviors or behavioral intentions of physicians. Only a few recent studies have explored the relationships between health beliefs and practice patterns in physician populations.¹¹ These findings may imply that before some pediatricians can be expected to change their practice patterns, they might have to undergo significant changes in their personal beliefs regarding how people

get sick or stay healthy. Such pediatricians may be identifiable on the basis of their personal beliefs about how one becomes and stays healthy.

Finally, another implication of our findings is that there needs to be a significant expansion of training activities directed toward increasing the knowledge and skills of medical students and residents related to mental health-oriented services,¹² an area of training in which most pediatricians believe they have received inadequate preparation.¹³

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Advising Parents to Stop Smoking

Opportunities and Barriers in Pediatric Practice

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• All pediatricians in Maine were surveyed by mail to assess their beliefs and attitudes about parental smoking and their current activities concerning advice on smoking cessation. The response rate to three mailings was 86%. Most pediatricians (91%) reported advising parents who smoke to quit and estimated spending an average of almost 5 minutes giving advice on how to quit smoking. Almost all pediatricians (94%) felt moderately or very confident in addressing passive smoking issues. However, only 46% felt moderately or very confident in advising parents how to stop smoking. Important barriers to providing advice on smoking cessation to parents included negative parental expectations and not having enough time. Only 6% of the pediatricians noted lack of reimbursement as a barrier. The majority of respondents (84%) were moderately or very willing to learn brief methods of giving advice on how to stop smoking to parents.

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The Surgeon General has suggested that one of the pediatrician's most important educational obligations is to encourage and help parents give up cigarette smoking.¹ Pediatricians are in a unique position to address the issues of smoking prevention and smoking cessation at several levels. Healthy young adults who are starting a family see a pediatrician more often than any other health care professional. Of the 3.6 to 3.7 million women who have given birth in the United States each year since 1980, approximately 1.0 to 1.2 million women smoked while pregnant.² In addition, the majority of women who give up smoking during pregnancy start

smoking again after the baby is born.³ New parents are motivated to make changes in their own life-styles "for the good of the baby." The pediatrician usually sees the mother shortly before and after delivery of the baby and at regular intervals over the next few weeks, months, and years for health supervision and other visits. Each of these contacts could provide an opportunity to support a smoker in her efforts to quit or to support a recent ex-smoker in her efforts to refrain from starting again. Women who succeed in staying away from cigarettes will then model non-smoking behavior for their children.

The purpose of this study was to assess the current activities of pediatricians concerning their provision of smoking cessation advice for the parents of the children in their office practices, their beliefs and attitudes about the effects of passive smoking and the initiation of smoking in children and adolescents, their confidence in their ability to offer advice about smoking, the opportunities and perceived barriers to providing advice to stop smoking, and their willingness to learn methods of providing advice about smoking prevention and smoking cessation.

SUBJECTS AND METHODS

A questionnaire was developed to address the factors that might influence pediatricians to provide advice on smoking cessation to the parents of their pediatric patients. The questionnaire contained 50 items and addressed the pediatrician's estimate of the proportion of smoking parents with whom smoking is discussed, the pediatrician's concerns about parental smoking, their level of confidence in discussing the effects of parental smoking on children, the estimated proportion of parents advised to stop smoking and the time spent advising parents about quitting, their level of confidence in advising parents how to quit, and their level of willingness to learn brief methods of providing advice on smoking ces-

sation to parents. Further items addressed whether the office had a policy on smoking, the availability in the office of printed materials about smoking cessation, and a list of the available smoking cessation resources within the community. Additional questionnaire items addressed the perceived barriers to giving advice to parents who smoke, beliefs about the effects of parental smoking on children, and the opportunities pediatricians have to address the smoking issue with parents. Final questions inquired about smoking status, year of graduation from medical school, number of years in pediatric practice, pediatric subspecialty, and type of practice.

We pretested this survey instrument among the pediatric faculty at the Maine Medical Center, Portland, mailing the questionnaire to the pediatricians there and obtaining a response rate of 93%. After reviewing these responses, we surveyed all the remaining licensed pediatricians in the state of Maine using the same instrument. Second and third mailings were sent to non-respondents.

We examined the frequency of responses to each item and also the relationships among responses. For the items addressing attitudes toward the effects of parental smoking and the ratings of opportunities to advise parents to stop smoking, we devised simple scales by summing the responses to these items. Because most of these data are categorical, we used χ^2 analyses to identify significant relationships using a $P < .05$ as the level of statistical significance. For continuous variables, we grouped the responses into categories for comparison with the categorical responses.

RESULTS

In 1987, we mailed the questionnaire to 155 pediatricians and received 139 responses for a return rate of 89.7%. We excluded physicians who had retired ($n=16$), who reported they were no longer practicing in Maine, or who were in research or administration ($n=23$). With these exclusions, we had 100 respondents. We have assumed that the 16 nonrespondents were in active prac-

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tice in Maine, for a response rate of 86.2% (100/116).

Pediatricians

On average, the respondent pediatricians, 34% of whom were women, had been in practice for 11.7 years (range, 1 to 40 years). Forty-six percent were in solo practice, 25% were in a partnership, 12% were hospital based, 7% were in group practices, 2% were in a community health center, and 8% were in other types of practice; 33% of all the respondents were on the faculty at the Maine Medical Center. Although 41% of the pediatricians had a subspecialty in pediatrics, the majority of these (74%) also saw patients for general pediatric problems. Only 4% were current smokers, 30% were former smokers, and 66% had never smoked.

Attitudes and Beliefs

Most pediatricians agreed or strongly agreed that parental smoking led to more respiratory infections (98%) and more ear infections (68%) in children and increased the chances that children will become smokers (94%). Many (65%) agreed that advice about smoking should be given to parents who smoke even when they bring their child to the pediatrician for problems unrelated to smoking.

Current Activities

Pediatricians' estimates of the proportion of parents who smoke ranged from about 10% to 50% or more, with the majority (72%) of respondents' estimates being about 25% or 33%. Most pediatricians (72%) estimated that they talk to 25% or more of the parents who smoke about the effects of smoking on their children, with 43% talking to three fourths or more of these parents. The major concerns addressed by the pediatricians were lower birth weight, the health effects of passive smoking on infants, parental modeling of smoking, the effects on parental health, and smoking-related environmental hazards such as fires and burns.

Most pediatricians (91%) reported advising parents who smoke to quit, with two thirds of the pediatricians advising 75% or more of such parents to do so. The average estimated proportion of parents advised to quit was 71.2%

Characteristics	Sample Size	Moderately or Very Confident in Advising Parents to Stop Smoking, %
Rating of opportunities to provide advice to parents to stop smoking		
High	48	60*
Low	37	30
Perceived barriers to talking to parents about smoking		
None	33	67*
≥1	62	35
Parents do not expect me to give this sort of advice		
Not checked	68	57*
Checked	27	19

* $P < .01$.

(SD = 39.8%). The estimated time spent advising parents to quit, for those pediatricians (89%) who provided such an estimate, averaged 4.9 minutes (SD = 4.6 minutes). Seventy-four percent of the respondents who advised parents to stop smoking did not provide an estimate of the effectiveness of their advice; for the 26 pediatricians who did, the estimated successful rate of cessation ranged from 1% to 75%, with a mode of 10%.

Almost all pediatricians (94%) felt moderately (43%) or very confident (51%) in addressing smoking issues with parents, but only 46% of pediatricians felt moderately (28%) or very confident (18%) in advising parents to quit. Most pediatricians (92%) had a "no smoking" policy in their offices; 31% had lists of available smoking cessation resources in the community, and 25% had printed materials to give smokers to help them quit.

Opportunities to Talk to Parents About Smoking

Pediatricians were asked to rate various types of visits as poor, fair, good, or excellent opportunities to talk to or advise parents who smoke about stopping the habit. Prenatal visits, health supervision visits, and visits for acute respiratory problems were rated as good or excellent opportunities by 83%, 77%, and 87% of the respondents, respectively. Visits to the mother at delivery and visits for other problems were rated as good or excellent opportunities by smaller proportions of pediatricians, 67% and 37%, respectively. Pediatricians who rated these potential oppor-

tunities more highly also reported advising a significantly greater proportion of parents to quit than those who rated them less highly ($P < .01$).

Barriers to Providing Advice About Smoking to Parents Who Smoke

Twenty-four percent of the pediatricians thought that parents who smoke do not expect this advice from their pediatrician, while "not having enough time" was noted as a barrier to giving advice on smoking cessation by 23% of the respondents. Some pediatricians were concerned that parents would get defensive and might even change pediatric practices if offered such advice. Ten percent of the respondents felt ill at ease about giving such advice and 6% considered lack of reimbursement to be a barrier. Only 3% of the pediatricians believed that the effects on the child were not serious enough to warrant giving advice on smoking cessation to parents, and a similar proportion believed that giving advice about smoking was none of their business.

One or more barriers were identified by 65% of pediatricians, and these respondents were significantly less likely to advise parents to stop smoking than were pediatricians who identified no barriers ($P < .01$). Pediatricians who identified "parents not expecting this advice" as a barrier also reported advising significantly fewer parents to quit smoking ($P = .02$).

Confidence in Advising Parents to Stop Smoking

Higher ratings of the opportunities to provide advice to parents to stop smok-

Table 2.—Willingness of Pediatricians to Learn Brief Methods of Smoking Cessation Advice for Parents

Characteristics	Sample Size	Very Willing to Learn Brief Methods of Advising Parents to Stop Smoking, %
Years in pediatric practice		
<5	45	40*
6-10	35	57
>10	15	33
Smoking status		
Never smoked	64	55*
Current or former smoker	32	28
Rating of opportunities to provide advice to parents about smoking		
High	47	62†
Low	38	26
Perceived barriers to talking to parents about smoking		
None	34	68†
≥1	62	34

* $P<.05$.

† $P<.01$.

ing, not checking any of the barriers to talking to parents about smoking, and not checking "parents do not expect me to give this sort of advice" were each associated with higher levels of confidence in advising parents to stop smoking ($P<.01$) (Table 1).

Willingness to Learn Brief Methods of Advice

The majority of respondents (84%) were either moderately (38%) or very (46%) willing to learn brief methods of giving advice about stopping smoking to parents. Pediatricians who had fewer years of experience in pediatric practice were more willing to learn methods of smoking cessation for parents as compared with more experienced pediatricians ($P<.02$). There was no difference in "willingness" based on the type of practice. Pediatricians who identified themselves as smokers or ex-smokers were less willing to learn brief methods of advice on smoking cessation for parents than were those who had never smoked ($P<.02$). The level of willingness of the pediatricians to learn brief methods of giving advice on smoking cessation to parents was significantly and directly related to their rating of the opportunities to talk to parents about stopping the habit ($P<.01$) and to not identifying any barriers to giving advice about smoking to parents who smoke ($P<.01$) (Table 2).

COMMENT

The results reported herein are based on a high response rate (86%) to the three mailings of the questionnaire and are thus reasonably representative of the pediatricians practicing in the state of Maine. The pediatricians' estimates of the proportion of parents who smoke whom they advised to stop should be interpreted with some caution. Self-reporting may overestimate the proportion of physicians who claim they advise patients to stop smoking,⁴ and we do not have information from the parents. Nevertheless, some important observations can be made.

A large proportion of pediatricians report talking to parents about the effects of smoking on their children, and their concerns about these effects reflect the literature on passive smoking and parental role modeling.⁵⁻⁹ The vast majority of pediatricians report advising most parents to stop smoking, with two thirds reporting advising 75% or more of such parents to stop. The pediatricians' estimates of the proportion of parents advised to stop smoking varied widely, but the mean value, 71.2%, is close to that reported by healthy smokers attending university-based outpatient clinics (58%)¹⁰ and by other patients (60%).¹¹

The average reported time spent advising parents to quit was almost 5 minutes, with a range of 1 to 20 minutes.

These estimates of the time spent talking about smoking are comparable with those reported by Iowa physicians (median, 5 minutes; range, 1 to 30 minutes) and to patients' reports of the number of minutes their physicians spent talking about smoking in medical settings.^{12,13}

Use of the prenatal visit, health supervision visits, and visits for respiratory problems, which pediatricians considered the best opportunities to talk to parents about stopping smoking, and providing self-help materials and lists of available community smoking cessation resources to smokers would encourage and assist parents in their efforts to quit.

Hughes and Kottke¹⁴ identified five major reasons for physicians failing to ask patients to quit—not believing the advice is worthwhile, not having the time to give advice, feeling that counseling is not a physician activity, not wanting to embarrass patients or discourage them from returning, and not realizing that advising patients to quit smoking can be simple. Of these potential barriers, the time concern was checked as a barrier by about one fourth of the respondent pediatricians. The perception that parents who smoke do not expect this advice from their pediatricians was also checked by about one fourth of the respondents. When other comparable concerns about potential parental responses to advice on smoking cessation, such as getting defensive or changing pediatric practices, are added to the perception of parents' lack of expectation, barriers of this kind were noted by 30% of the pediatricians. Only three of the pediatricians believed that the effects of smoking on the child were not serious enough to warrant giving advice on smoking cessation to parents. The pediatricians' report of the high proportion of parents given advice on smoking cessation and the time spent doing this indicate that the vast majority believe that giving advice to stop smoking is worthwhile. Similarly, only three pediatricians considered that giving advice about smoking was none of their business, indicating that the vast majority do consider that giving advice about smoking to parents is a pediatrician activity. We did not have an item addressing Hughes and Kottke's fifth reason for not giving advice to patients about quit-

ting smoking. We also have no information yet as to how smoking parents themselves feel about receiving advice on quitting smoking from their pediatricians.

Pediatricians reported high levels of confidence in talking to parents about the effects of smoking on their children but had less confidence in advising parents to quit. Surveys of other physicians have also noted low levels of confidence in providing advice on smoking cessation.¹⁵⁻¹⁷ Most pediatricians provided no estimate of the success rate of their advice to quit smoking, but for those who did, the modal estimate was 10%. Success rates of this order after physician-delivered advice on smoking cessation have been reported from a number of studies. In a recently reported meta-analysis of 39 trials of advice on smoking cessation or counseling carried out in physicians' offices, the average reported rate of quitting after 1 year in the intervention groups was 5.8% higher than that in the control groups.¹⁸ Even a sustained rate of quitting as low as 5%, as reported by Russell and colleagues¹⁹ in 1979 using brief (2-minute) advice on smoking cessation, supportive printed material and follow-up (which was more effective than brief advice alone, 3.3%), would produce a large number of those who quit if all primary care practitioners engaged in this behavior. It has been shown that persuading as few as 1 in 20 smokers to quit compares favorably in cost-effectiveness to treating individual patients for hypertension or hypercholesterolemia.²⁰

As might be expected, there were generally high levels of willingness to learn brief methods of providing advice on smoking cessation to parents. This high level of willingness by pediatricians to learn methods of giving advice on smoking cessation is consistent with other reports concerning interest by primary care physicians in acquiring skills to help patients change their behavior.^{4,21} The confidence of physicians about their abilities to help patients stop smoking can be increased if they are given support, such as physician training, referral information, monetary reimbursement, literature to hand out, or the ability to hire or train staff to help.¹⁶

Perry and Silvis²² stress that pediatricians need to learn the skills to promote

nonsmoking and to encourage attempts to quit by parents and adolescents. They also need to motivate themselves to use these skills. In designing workshops or in-office training for pediatricians to enhance their skills in providing advice on smoking cessation to parents, we see several areas that need addressing. The barrier of perceived negative parental expectations needs to be resolved by asking parents what they think about their pediatricians advising them to stop smoking. The advice or counseling clearly needs to be delivered in about 5 minutes but also must be presented in such a fashion that the process of quitting and staying away from cigarettes can be brought up at each visit, if necessary. The important components of advice on smoking cessation for use in office practice, which can be delivered in 3 to 5 minutes, have been described by several authors.^{11,19,20,23-25} Most importantly, such training sessions should involve modeling the advice either live or on videotape and role playing the type of advice that can be given with appropriate feedback. Such modeling and role playing substantially increase confidence in one's ability to undertake these new skills and increase the likelihood that such advice will be given. Pediatricians are in an excellent position to incorporate advice on smoking cessation for parents into routine care, and by enhancing their skills in providing such advice, they may contribute more effectively to the concerted effort to help smokers stop smoking.

This project was supported in part by grant CA22453 from the Public Health Service, National Cancer Institute, Bethesda, Md.

Paul Dymont, MD, helped us to carry out the initial survey among the Pediatric Faculty at the Maine Medical Center.

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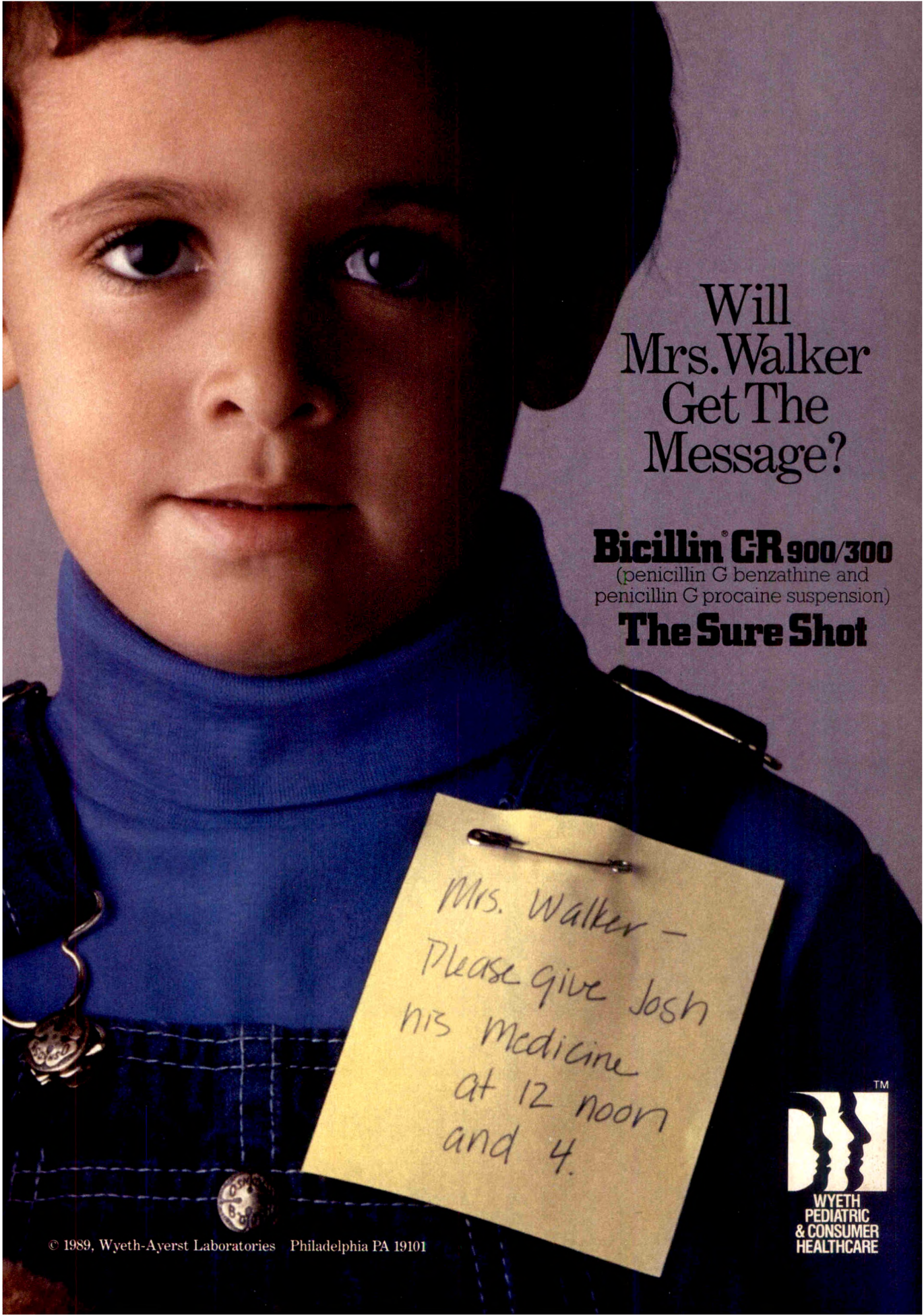
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Get The
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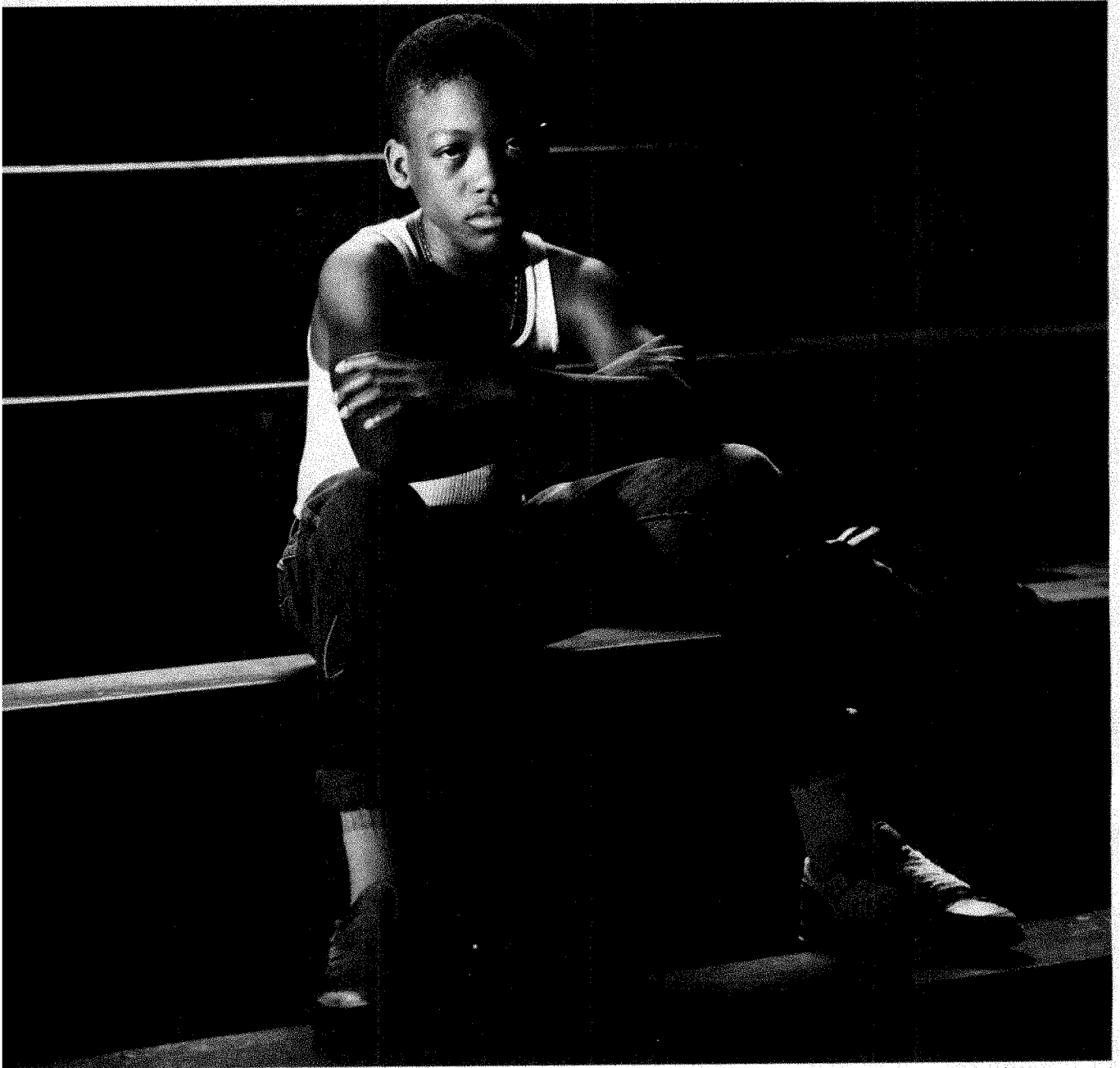
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6/89

BRIEF SUMMARY

VIST®

nastine fumarate) SYRUP 0.5 mg/5 ml
sent as clemastine fumarate 0.67 mg/5 ml)

INDICATIONS AND USAGE

ist® (clemastine fumarate) Syrup is indicated for the relief of symptoms associated with allergic rhinitis such as sneezing, rhinorrhea, pruritus and lacrimation. Tavist® (clemastine fumarate) Syrup is indicated for use in pediatric populations (ages 6 through 12) and adults (see **DOSAGE AND ADMINISTRATION**).

It should be noted that Tavist® (clemastine fumarate) is indicated for the relief of mild, uncomplicated allergic skin manifestations of urticaria and angioedema at the 2 mg dosage level.

CONTRAINDICATIONS

Antihistamines are contraindicated in patients hypersensitive to the drug or to other antihistamines of similar chemical structure. **PRECAUTIONS — Drug Interactions** in a complete package insert).

Antihistamines should not be used in newborn or premature infants. Because of the higher risk of antihistamines for infants and for newborns and prematures in particular, antihistamine therapy is contraindicated in nursing mothers (see **PRECAUTIONS — Nursing Mothers** in a complete package insert).

WARNINGS

Antihistamines should be used with considerable caution in patients with: narrow angle glaucoma, stenosing peptic ulcer, duodenal obstruction, symptomatic prostatic hypertrophy, bladder neck obstruction.

With CNS Depressants: Tavist® (clemastine fumarate) additive effects with alcohol and other CNS depressants (barbiturates, sedatives, tranquilizers, etc.).

In Activities Requiring Mental Alertness: Patients should be warned about engaging in activities requiring mental alertness such as driving a car or operating appliances, machinery.

In the Elderly (approximately 60 years or older): Antihistamines are more likely to cause dizziness, sedation, and anxiety in elderly patients.

ADVERSE REACTIONS

Most frequent adverse reactions are underlined:

Central Nervous System: Sedation, sleepiness, dizziness, disturbed nation, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesia, dizziness, diplopia, vertigo, tinnitus, acute labyrinthitis, hyperreflexia, convulsions.

Gastrointestinal System: Epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.

Respiratory System: Thickening of bronchial secretions, wheezing, chest and wheezing, nasal stuffiness.

Cardiovascular System: Hypotension, headache, palpitations, tachycardia, extrasystoles.

Hematologic System: Hemolytic anemia, thrombocytopenia, leukocytosis.

Genitourinary System: Urinary frequency, difficult urination, urinary retention, early menses.

Other: Urticaria, drug rash, anaphylactic shock, photosensitivity, excessive perspiration, chills, dryness of mouth, nose, throat.

DOSAGE AND ADMINISTRATION

DOSAGE SHOULD BE INDIVIDUALIZED ACCORDING TO CLINICAL NEEDS AND RESPONSE OF THE PATIENT.

Indications: Children aged 6 to 12 years

Symptoms of Allergic Rhinitis — The starting dose is 1 teaspoonful (0.5 mg clemastine) twice daily. Since single doses of 2.25 mg clemastine were well tolerated by this age group, dosage may be increased as required, but not to exceed 2.25 mg clemastine daily (3 mg clemastine).

Urticaria and Angioedema — The starting dose is 2 teaspoonful (1 mg clemastine) twice daily, not to exceed 6 teaspoonful daily (3 mg clemastine).

Indications: Adults and Children 12 Years and Over

Symptoms of Allergic Rhinitis — The starting dose is 1 teaspoonful (1 mg clemastine) twice daily. Dosage may be increased as required, but not to exceed 12 teaspoonful daily (6 mg clemastine).

Urticaria and Angioedema — The starting dose is 4 teaspoonful (2 mg clemastine) twice daily, not to exceed 12 teaspoonful daily (6 mg clemastine).

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[TAS-Z3 APRIL 1, 1986]

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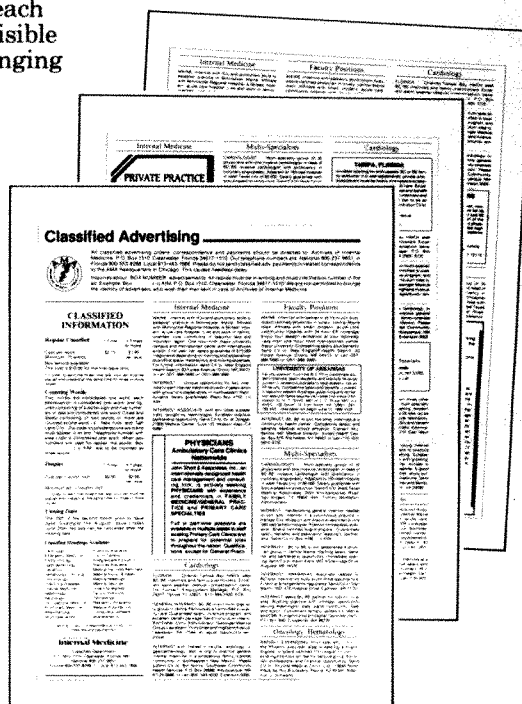
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Radiological Case of the Month

Christina T. Giuliano, MD; Abraham Zerykier, MD; Jack O. Haller, MD (*Contributors*);
Beverly P. Wood, MD (*Section Editor*)

A 12-year-old Asian boy with a diagnosis of acute lymphocytic leukemia received induction chemotherapy with good response. One month later, during the intensification phase of his chemotherapy, he was admitted to the hospital for abdominal pain.

On physical examination he appeared to be in poor physical health with generalized abdominal tenderness. Abnormal laboratory values included an erythrocyte sedimentation rate of 66 mm/h, and elevated amylase, aspartate aminotransferase, and alkaline phosphatase levels. The patient continued to reach temperatures of 39.4°C, despite antibiotic therapy with cephalothin, gentamicin sulfate, and carbenicillin disodium. His condition deteriorated, and he was taken to the operating room for exploratory laparotomy following computed tomographic (Fig 1) and gallium 67 citrate (Fig 2) studies.

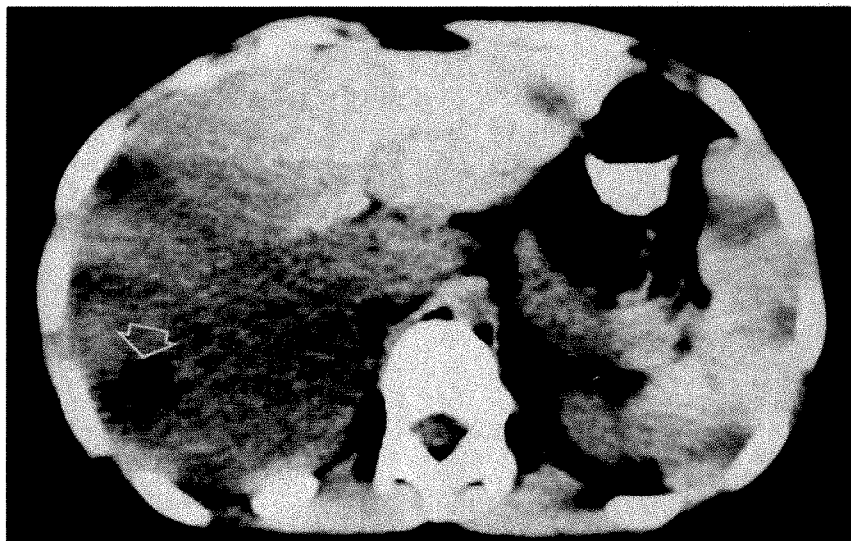
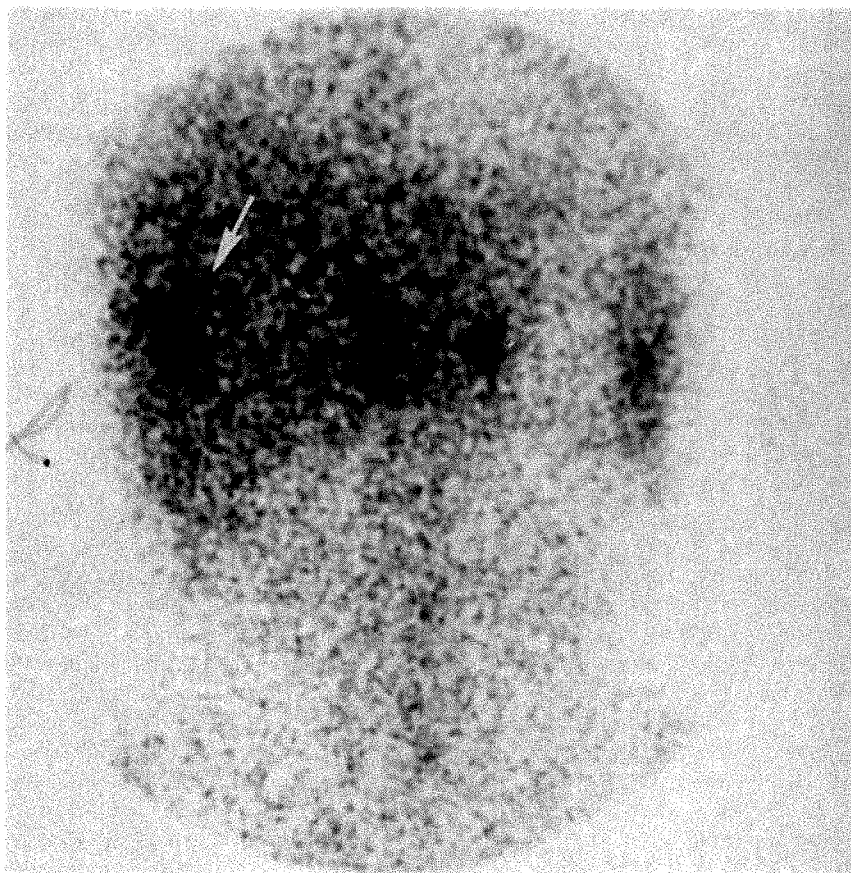


Figure 1.

Figure 2.



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Contributed from the Department of Radiology, Downstate Medical Center (Drs Giuliano and Haller), and the Department of Pediatrics, The Long Island College Hospital (Dr Zerykier), Brooklyn, NY.

Reprint requests to Department of Radiology, PO Box 648, University of Rochester Medical Center, 601 Elmwood Ave, Rochester, NY 14642 (Dr Wood).

Pylephlebitis Secondary to Unsuspected Appendiceal Rupture

Fig 1.—Computed tomographic scan of the liver showing a low attenuation area (arrow) in the posterior right lobe of the liver.

Fig 2.—Gallium 67 citrate scan showing an area of increased uptake in the corresponding region of the liver (arrow).

On exploratory laparotomy, the patient was found to have a ruptured appendix with microabscess formation in both lobes of the liver (pylephlebitis), an unusual complication of appendicitis rarely seen in the current era of antibiotics.

One week prior to admission, the patient had completed a course of induction chemotherapy consisting of vincristine sulfate, L-asparaginase, intrathecal methotrexate sodium, and prednisone. Postoperatively, his course was uncomplicated and uneventful. He resumed chemotherapy following his release from the hospital and has had a complete remission of acute lymphocytic leukemia. He is currently doing well, with no evidence of disease.

Pylephlebitis may be caused by any primary inflammatory disease in which suppurative tissue is drained by portal vein tributaries. One may see it secondary to a variety of intra-abdominal inflammatory processes within the gastrointestinal tract (appendicitis), pancreatic or biliary system, spleen, umbilical vein of neonates, or urogenital tract. It is rare that foreign bodies puncturing viscera drained by the portal tree or that the portal vein or its branches directly may cause pylephlebitis.¹ The high mortality associated with hepatic abscess (50% overall, 80% when secondary to causes other than appendicitis) make it important to recognize the presence of pylephlebitis.²

Pathologically, thrombophlebitis occurs in the intra-abdominal vessels of an infected viscus. This may progress to involve the draining veins with thrombotic extension along the portal route. Bacteria reach the liver and subsequently the portal triads, which

become infected both within and around the lymphatics. Polymorphonuclear leukocyte invasion and cellular debris extend directly into the hepatic lobular parenchyma. The resulting pyogenic liver abscesses may be found in one or both hepatic lobes and may be solitary, be confluent, or consist of multiple small abscesses diffusely distributed. Ochsner et al³ described multiple abscesses in 45% of their patients. Balasegaram⁴ found these lesions to be five times more common in the right lobe as compared with the left. This distribution is postulated to be the result of blood flow, with the abscess localized to the lobe that receives drainage from the primary site of infection. The right lobe receives a greater volume of blood, also contributing to the higher frequency of abscess found there.⁴

Classically, these patients present with hyperpyrexia, abdominal pain, and malaise. A leukocytosis is often evident. However, as 30% of hepatic abscesses are seen in leukemic children receiving immunosuppressive chemotherapy, suspicion must be raised when these neutropenic patients develop fever that is unresponsive to antibiotics.⁵

The diagnostic workup begins with roentgenograms, which sometimes reveal right basilar pulmonary atelectasis, hepatomegaly, or air-fluid levels in an abscess cavity within the right upper quadrant.

A computed tomographic scan of the abdomen is useful to delineate focal lesions in the hepatic parenchyma. An abscess in the liver may be identified as a low-attenuation focus, with contrast-enhancing thick borders. Small microabscesses appear as multiple, diffuse, low-attenuation lesions. These

are more commonly seen in immunosuppressed patients.

The differential diagnosis for the appearance of this computed tomographic scan includes cysts, liver adenoma, focal nodular hyperplasia, and intrahepatic or subcapsular mucinous metastases from the colon or ovary. Loops of bowel adjacent to the liver may mimic the appearance of a hepatic abscess.

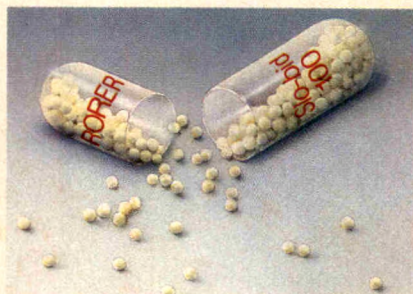
To further clarify the nature of the lesion, a ⁶⁷Ga citrate nuclear scan is useful. ⁶⁷Ga has a high avidity for localized pyogenic disease, with a detection rate of 90%, and is currently the agent of choice for imaging suppurative inflammatory disease.⁶

When severe pylephlebitis is suspected, ultrasonography is also a useful tool to evaluate the portal venous network. This has successfully identified (1) echogenic thrombus in the lumen of the portal vein; (2) the existence of portal vein collateral circulation; (3) enlargement of an already thrombosed vein; and (4) cavernous transformation of the portal vein.⁷

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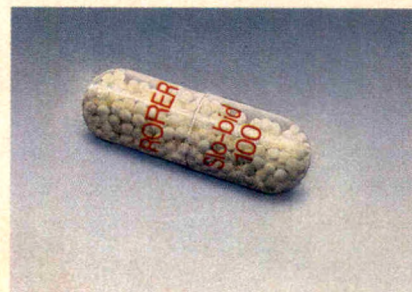
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Growing up on a steady theophylline is an open-and-shut case



Sprinkled

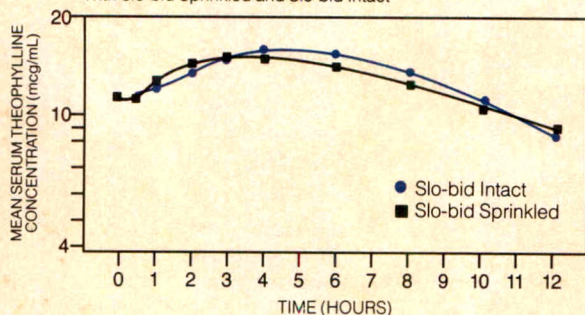
Intact



Changing your patients from sprinkled to solid theophylline administration shouldn't mean changing their serum levels as well. With Slo-bid, you won't change a thing when your younger asthma patients are ready to switch to intact administration.

Slo-bid maintains steady theophylline levels when switching from sprinkled to solid administration¹

Mean Serum Theophylline Concentration in 14 Children Dosed With Slo-bid Sprinkled and Slo-bid Intact



Switching from Slo-bid sprinkled to Slo-bid intact causes virtually no change in serum levels. Since the release system doesn't change, theophylline performance with both forms is identical. There's no need to restabilize your patients when they switch to taking capsules. In addition, capsules are the dosage form more patients prefer to take.²

Keep your patients' theophylline levels steady. Start and stay with Slo-bid. It's the perfect theophylline system for asthma patients to grow up with.

References: 1. Saccar CL, Gawchik S, Spitzer I, et al: Steady-state evaluation of sustained-release theophylline administered in apple-sauce in asthmatic children. *Immunol Allergy Pract* 1987;9:462-466. 2. Consumer attitudes toward solid forms of medication. Capsugel, Division of Warner-Lambert Company, March 1983.

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Slo-bid™

(theophylline, anhydrous)

50 mg, 75 mg, 100 mg, 125 mg, 200 mg, and 300 mg

Gyrocaps®

Timed-Release Capsules

BRIEF SUMMARY

DESCRIPTION: Slo-bid™ Gyrocaps® contain 50 mg, 75 mg, 100 mg, 125 mg, 200 mg, or 300 mg theophylline, anhydrous in the form of long-acting beads within a dye-free hard gelatin capsule and are intended for oral administration. Slo-bid Gyrocaps can be administered with a 12-hour dosing interval for a majority of patients and a 24-hour dosing interval for selected patients (see DOSAGE AND ADMINISTRATION section in full prescribing information for description of appropriate patient population).

INDICATIONS AND USAGE: For relief and/or prevention of symptoms from asthma and reversible bronchospasm associated with chronic bronchitis and emphysema.

CONTRAINDICATIONS: Slo-bid is contraindicated in individuals who have shown hypersensitivity to any of the components of this product. It is also contraindicated in patients with active peptic ulcer disease and in individuals with underlying seizure disorders (unless receiving appropriate anticonvulsant medication).

WARNINGS: Serum levels above 20 µg/mL are rarely found after appropriate administration of the recommended doses. However, in individuals in whom theophylline plasma clearance is reduced for any reason, even conventional doses may result in increased serum levels and potential toxicity. Reduced theophylline clearance has been documented in the following readily identifiable groups: 1) patients with impaired renal or liver function; 2) patients over 55 years of age, particularly males and those with chronic lung disease; 3) those with cardiac failure from any cause; 4) patients with sustained high fever; 5) neonates and infants under 1 year of age; and 6) those patients taking certain drugs (see PRECAUTIONS, Drug Interactions). Frequently, such patients have markedly prolonged theophylline serum levels following discontinuation of the drug.

Reduction of dosage and laboratory monitoring is especially appropriate in the above individuals.

Serious side effects such as ventricular arrhythmias, convulsions, or even death may appear as the first sign of toxicity without any previous warning. Less serious signs of theophylline toxicity (i.e., nausea and restlessness) may occur frequently when initiating therapy but are usually transient; when such signs are persistent during maintenance therapy, they are often associated with serum concentrations above 20 µg/mL. Stated differently, *serious toxicity is not reliably preceded by less severe side effects.* A serum concentration measurement is the only reliable method of identifying a potential for life-threatening toxicity.

Many patients who require theophylline exhibit tachycardia due to their underlying disease process, so the cause/effect relationship to elevated serum theophylline concentrations may not be appreciated.

Theophylline products may cause dysrhythmia and/or worsen preexisting arrhythmias and any significant change in rate and/or rhythm warrants monitoring and further investigation.

Studies in laboratory animals (minipigs, rodents, and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

PRECAUTIONS: General: On the average, theophylline half-life is shorter in cigarette and marijuana smokers than in nonsmokers, but smokers can have half-lives as long as nonsmokers. Theophylline should not be administered concurrently with other xanthine preparations. Use with caution in patients with hypoxemia, hypertension or with a history of peptic ulcer. Theophylline may occasionally act as a local irritant to the GI tract, although GI symptoms are more commonly centrally mediated and associated with serum drug concentrations over 20 µg/mL.

Information for Patients:

The physician should reinforce the importance of taking only the prescribed dose at the prescribed time intervals. The patient should alert the physician if symptoms occur repeatedly, especially near the end of a dosing interval. When prescribing administration by the sprinkle method, details of the proper technique should be explained to the patient.

Laboratory Test: Serum levels should be monitored periodically to determine the theophylline levels associated with observed clinical response and to identify the potential for toxicity. For such measurements, the serum sample should be obtained at the time of peak concentration, approximately 5-9 hours after the morning dose. It is important that the patient has not missed or taken additional doses during the previous 48 hours and that dosing intervals have been reasonably equally spaced.

DOSE ADJUSTMENT BASED ON SERUM THEOPHYLLINE MEASUREMENTS WHEN THESE INSTRUCTIONS HAVE NOT BEEN FOLLOWED MAY RESULT IN RECOMMENDATIONS THAT PRESENT RISK OF TOXICITY TO THE PATIENT.

Drug Interactions:

Drug-Drug: Toxic synergism with ephedrine has been documented and may occur with some other sympathomimetic bronchodilators. In addition, the following drug interactions have been demonstrated:

Theophylline with:
Allopurinol (high dose)

Increased serum theophylline levels

Cimetidine

Increased serum theophylline levels

Erythromycin, Troleandomycin

Increased serum theophylline levels

Lithium carbonate

Increased renal excretion of lithium

Oral contraceptives

Increased serum theophylline levels

Phenytoin

Decreased theophylline and phenytoin serum levels

Rifampin

Decreased serum theophylline levels

Drug-Food: Taking Slo-bid immediately after a high-fat content meal such as 8 ounces whole milk, 2 fried eggs, 2 strips bacon, one bran muffin with butter, 2 ounces hash brown potatoes (about 789 calories, including approximately 49 gm of fat) may result in a decrease in the rate of absorption, but with no significant difference in the extent of absorption (see CLINICAL PHARMACOLOGY, Pharmacokinetics). The influence of the type and amount of other foods, as well as the time interval between drug and food, has not been studied.

Drug/Laboratory Test Interactions: Currently available analytic methods, including high-pressure liquid chromatography and immunoassay techniques, for measuring serum theophylline levels are specific. Metabolites and other drugs generally do not affect the results. Other new analytic methods are also now in use. The physician should be aware of the laboratory method used and whether other drugs will interfere with the assay for theophylline.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies have not been performed with theophylline.

Chromosome-breaking activity was detected in human cell cultures at concentrations of theophylline up to 50 times the therapeutic serum concentrations in humans. Theophylline was not mutagenic in the dominant lethal assay in male mice given theophylline intraperitoneally in doses up to 30 times the maximum daily human oral dose.

Studies to determine the effect on fertility have not been performed with theophylline.

Pregnancy: Pregnancy Category C—Animal reproduction studies have not been conducted with theophylline. It is also not known whether theophylline can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Theophylline should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Theophylline is distributed into breast milk and may cause irritability or other signs of toxicity in nursing infants. Because of the potential for serious adverse reactions in nursing infants from theophylline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:

Safety and effectiveness of Slo-bid Gyrocaps administered:

1. Every 24 hours in children under 12 years of age, have not been established.
2. Every 12 hours in children under 6 years of age, have not been established.

ADVERSE REACTIONS: The following adverse reactions have been observed, but there has not been enough systematic collection of data to support an estimate of their frequency. The most consistent adverse reactions are usually due to overdosage.

Gastrointestinal: nausea, vomiting, epigastric pain, hematemesis, diarrhea.

Central Nervous System: headaches, irritability, restlessness, insomnia, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions.

Cardiovascular: palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, ventricular arrhythmias.

Respiratory: tachypnea

Renal: potentiation of diuresis.

Other: alopecia, hyperglycemia, inappropriate ADH syndrome, rash.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription. Keep this and all medications out of the reach of children.

NOW SUPPLIED:

Slo-bid Gyrocaps are identified as follows:

50 mg—Clear (cap) and opaque white (body) capsule with 50 printed in red

75 mg—Opaque white (cap) and clear (body) capsule with 75 printed in red

100 mg—Clear capsule with 100 printed in red

125 mg—Opaque white (cap) and opaque white (body) capsule with 125 printed in red

200 mg—Opaque white (cap) and clear (body) capsule with 200 printed in red

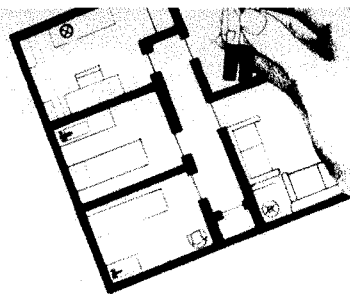
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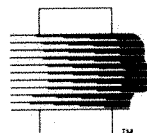
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Gastroesophageal Reflux to the Proximal Esophagus in Infants With Bronchopulmonary Dysplasia

Bruce D. Sindel, MD; M. Jeffrey Maisels, MB, BCh; Thomas V. N. Ballantine, MD

• **Recurrent aspiration after gastroesophageal reflux (GER) may contribute to the severity of chronic lung disease. If so, it should be possible to document acid reflux to the proximal esophagus. Using an esophageal pH probe placed at the level of the first or second thoracic vertebra, we evaluated GER in 14 infants with bronchopulmonary dysplasia (BPD) and 13 infants without BPD. The infants with BPD had significantly less GER, as measured by the percentage of time the pH was less than 4 ($3.26\% \pm 7.05\%$ vs $12.88\% \pm 15.27\%$ [mean \pm SD]), number of GER episodes per hour (0.46 ± 0.66 vs 1.35 ± 0.83), number of GER episodes lasting longer than 5 minutes per hour (0.10 ± 0.23 vs 0.31 ± 0.29), and longest GER episode (6.76 ± 10.29 vs 26.66 ± 38.30 minutes). Gastroesophageal reflux may be unimportant in infants with BPD, or even occasional episodes of GER may aggravate existing lung disease.**

(AJDC. 1989;143:1103-1106)

Gastroesophageal reflux (GER) has been implicated as a contributing factor in a variety of respiratory diseases in infants, including apnea,^{1,3} recurrent pneumonia,^{4,5} asthma,^{6,8} and bronchitis.^{9,10} Although the mechanism is unclear, it is most likely recurrent aspiration of refluxed material or reflex bronchospasm mediated by chemoreceptors in the esophagus, larynx, or trachea.

Infants with bronchopulmonary dysplasia (BPD) are often examined and treated empirically for GER, although there are no data documenting the inci-

dence of GER in these infants. Three recent reports¹¹⁻¹³ suggest that antireflux therapy might produce improvement in infants with BPD. We therefore studied a group of infants with BPD to determine the frequency of GER to the proximal esophagus, and we compared them with a group of infants without BPD.

PATIENTS AND METHODS

Patient Population

Infants with BPD diagnosed from March 1984 through January 1985 were eligible for the study. The diagnosis of BPD was made in infants who had severe lung disease, who required mechanical ventilation for more than 2 weeks or oxygen therapy for more than 1 month, and in whom the typical chest roentgenographic changes were present.¹⁴⁻¹⁷ We selected only those with moderate to severe disease (as defined by the necessity for mechanical ventilation for longer than 30 days or oxygen therapy for longer than 40 days) since we believed that GER was more likely to contribute to the severity of lung disease in such infants.

Fourteen infants met these criteria, and all manifested one or more of the following: (1) vomiting, (2) extreme irritability, (3) recurrent cyanotic episodes resembling aspiration, (4) deterioration of respiratory status during enteral feeding, and (5) stable or worsening respiratory status in the face of adequate energy intake and growth. Eight of these infants received mechanical ventilation and two of the eight were studied twice, once during ventilation and once while breathing spontaneously. All infants received ventilation through orotracheal tubes, and none received nasal continuous positive airway pressure during these studies. All infants received approximately 150 mL/kg of fluid per day. Infants receiving mechanical ventilation were fed 50% to 100% of this volume via an indwelling nasogastric tube. Feedings were given every 3 hours in volumes ranging from 9 to 19 mL/kg per feeding (depending on the volume tolerated) to all infants who were not receiving ventilator therapy.

The comparison group consisted of 12 infants who were being studied (on clinical indication) for episodes of apnea and bradycardia and one growing premature infant. These infants were studied with a four-channel thermister pneumocardiogram and an esophageal pH probe. They were all stable and free of respiratory symptoms (other than apnea) at the time of the study. They were not vomiting excessively and were free of conditions believed to increase GER, such as excessive vomiting, severe central nervous system insults, methylxanthine therapy, or feeding via nasogastric tube.

Patient data are provided in Table 1. Since BPD is more common in extremely premature and very-low-birth-weight infants, it is not surprising that the birth weight and gestational age were much lower in the BPD group. Infants with BPD were also older at the time of the study, although the mean postconceptual age was similar in the two groups.

The study was approved by the Clinical Investigation Committee of The Milton S. Hershey Medical Center, Hershey, Pa, and informed parental consent was obtained in the case of the growing premature infant.

pH Studies

We monitored upper esophageal pH continuously in all patients by means of an esophageal pH probe (Microelectrodes Inc 508, Londonderry, NH) with a diameter of 1.4 mm. Before each study, the probe was standardized at a pH of 2 and 7 then inserted nasally and positioned in the stomach to document that the gastric pH was less than 4.0 (which it was in all cases). The probe was then placed in the proximal esophagus at the level of T1-2, and the position was confirmed by roentgenograms (Figure). The standardization at a pH of 2 and 7 was repeated at the completion of each study, and drift of more than 0.3 pH units was cause for rejection of the study. This occurred only once, and the study was repeated the next day without incident.

In preliminary studies we found that infant formula and human breast milk will buffer gastric acid, raising the pH to more than 4.0

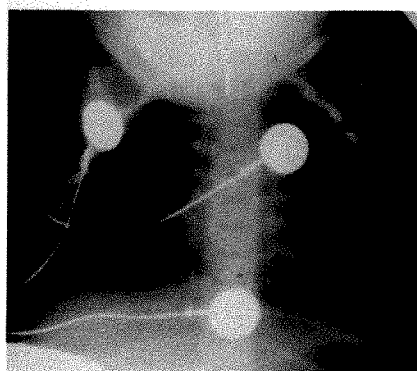
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Table 1.—Patient Data

	Patients With Bronchopulmonary Dysplasia	Patients Without Bronchopulmonary Dysplasia
No. of patients	14	13
Birth weight, g	1146 ± 606	2151 ± 1050
Gestational age at birth, wk	28.1 ± 4.0	34.2 ± 5.5
Age at time of study, d	72.9 ± 43.9	34.4 ± 22.0
Postconceptional age, wk	38.9 ± 7.2	39.1 ± 4.3



Chest roentgenogram showing pH probe in the proximal esophagus at the level of the second thoracic vertebra.

for up to 2.5 hours after a feeding. We therefore fed infants dextrose water during the study to maintain gastric acidity. Infants were studied supine. A few of the infants with BPD receiving assisted ventilation were temporarily placed in the prone position when deterioration in color or blood gases occurred (usually after chest physical therapy). They were returned to the supine position as soon as they were stable. Infants were studied for periods of 6 to 14 hours (long enough to include at least two feedings¹⁸; the duration of most studies was 12 hours). All data were recorded continuously on a recorder (Gould 2400) or a computer (Hewlett-Packard 9845B, Palo Alto, Calif) and analyzed by one of us (B.D.S.). A reflux episode was defined as a pH of less than 4 for at least 15 seconds. Esophageal acid clearance time (or average length of each GER episode) was calculated by dividing the total time of pH less than 4 by the number of reflux episodes. The data were not normally distributed and were analyzed by means of the Mann-Whitney *U* Test.

RESULTS

Reflux data are shown in Table 2. Infants with BPD had significantly less GER than did infants without BPD when measured by percentage of time pH was less than 4 ($P < .05$), number of

GER episodes per hour ($P < .01$), number of GER episodes longer than 5 minutes per hour ($P < .025$), and longest GER episode ($P < .05$). The value for esophageal acid clearance time was also lower in infants with BPD but was not significantly different ($P < .1$).

The effect of mechanical ventilation on the BPD group is shown in Table 3. Two of these infants were studied twice, once while receiving mechanical ventilation and once while breathing spontaneously. Although no significant differences were found, there was a consistent trend toward less GER in all measurements in infants who were being mechanically ventilated.

COMMENT

Although the pathogenesis of GER in association with respiratory diseases is unclear, several mechanisms have been proposed. The bulk of the data points to a stimulation of the laryngeal or tracheal chemoreceptors by refluxed stomach contents, causing a reflex bronchospasm or laryngospasm. Previous studies by Johnson and others^{19,21} have demonstrated the existence of taste bud-like laryngeal chemoreceptors in fetal lambs and newborn human infants. These studies demonstrate a "diving reflex" (laryngospasm, bradycardia, and redistribution of blood flow in favor of the brain, heart, and adrenals) in fetal animals when the laryngeal area is exposed to water or heterologous milk.

There is some evidence of existence of this "laryngeal chemoreflex" in human preterm infants with apnea.²² A recent study by Tuchman et al²³ demonstrated a significant increase in total lung resistance in adult cats after an infusion of a tiny amount of acid into the trachea. A similar response, although much smaller quantitatively, was produced by much larger acid infusion into the esoph-

agus. The authors postulated that "microaspiration in the trachea is a much more likely mechanism for bronchospasm associated with GER than simple acid-reflux into the esophagus." Herbst et al¹¹ were able to induce obstructive apnea in infants with BPD and apnea by instilling acid into the midesophagus. They also postulated that stimulation of laryngeal or pharyngeal chemoreceptors was the mechanism for the reflex laryngospasm. These data seem to implicate GER in the midesophagus as an important factor in the genesis of GER-associated respiratory disease.

Gastroesophageal reflux to the upper esophagus has been documented in infants with recurrent pneumonia,²⁴ while other studies have failed to find any correlation between GER as measured in the lower esophagus and respiratory disease²⁵ or apnea.²⁶ By means of extended lower esophageal pH monitoring, it has been shown that respiratory symptoms are associated with an increase in the mean duration of reflux (or esophageal clearance time) during sleep.²⁷ One could postulate that poor esophageal clearance while the subject is sleeping, and often supine, would likely cause the refluxed acid to reach the upper esophagus, larynx, or pharynx. We therefore decided to perform all of our pH studies in the upper third of esophagus.

Some clinicians have suggested that GER may contribute to the severity of chronic lung disease, although evidence of this is limited. We recently reported our experience in 10 infants with BPD who underwent antireflux surgery.¹² After surgery, 4 of the 5 infants receiving mechanical ventilation were weaned from it, and an additional 4 infants were weaned from oxygen therapy. The mean PCO₂ also decreased by 10 mm Hg. Herbst and coworkers¹¹ studied 14 infants with BPD who were found to have GER confirmed by barium esophagogram and the Tuttle test. Although they used apnea as a measure of illness in these infants, all infants required oxygen and 3 were being mechanically ventilated when antireflux therapy was initiated. By the end of 1 week, the apnea had improved, no patient was receiving ventilation therapy, and only 3 of 14 required oxygen. Our infants with BPD were generally sicker than those stud-

Table 2.—GER to the Proximal Esophagus in Infants With and Without BPD*

	Mean \pm SD (Median)		P
	Patients With BPD	Patients Without BPD	
% of time pH <4	3.26 \pm 7.05 (0.49)	12.88 \pm 15.22 (9.0)	<.05
No. of GER episodes/h	0.46 \pm 0.66 (0.32)	1.35 \pm 0.83 (1.33)	<.01
No. of GER episodes >5 min/h	0.10 \pm 0.23 (0)	0.31 \pm 0.29 (0.25)	<.025
Longest GER episode, min	6.76 \pm 10.29 (1.49)	26.66 \pm 38.30 (13.63)	<.05
Esophageal acid clearance time, min†	2.06 \pm 2.00 (1.37)	4.31 \pm 3.84 (2.69)	<.1

*GER indicates gastroesophageal reflux; BPD, bronchopulmonary dysplasia. A GER episode was defined as a pH of less than 4 for longer than 15 seconds.

†Average length of each GER episode, defined as the total time the pH was less than 4 divided by the total number of GER episodes.

Table 3.—GER to the Proximal Esophagus in Mechanically Ventilated and Spontaneously Breathing Infants With BPD*

	Mean \pm SD (Median)		P
	Ventilator	No Ventilator	
No. of patients†	8	8	...
% of time pH <4	0.98 \pm 1.75 (0.27)	4.74 \pm 9.14 (0.54)	>.1
No. of GER episodes/h	0.22 \pm 0.25 (0.17)	0.60 \pm 0.85 (0.35)	>.1
No. of GER episodes >5 min/h	0.01 \pm 0.03 (0)	0.16 \pm 0.30 (0)	>.1
Longest GER episode, min	4.67 \pm 10.02 (0.65)	7.26 \pm 10.11 (2.55)	<.1
Esophageal acid clearance time, min	1.31 \pm 1.63 (0.88)	2.42 \pm 2.17 (1.55)	<.1

*GER indicates gastroesophageal reflux; BPD, bronchopulmonary dysplasia.

†Fourteen infants were studied; 2 were studied both with and without mechanical ventilation.

ied by Herbst et al. Eight of the 14 infants we studied were being mechanically ventilated (and therefore not having apnea), and all of the infants had higher oxygen requirements than those in the previous report. However, we did not specifically record the number of apneic episodes per day in our infants.

Our infants with BPD had significantly less GER than did those without BPD. This finding is surprising, but it could be explained by several factors: Boix-Ochoa and Canals²⁸ showed that there is a maturational process involving the lower esophageal sphincter and that this is primarily dependent on chronologic age, but not on postconceptional age. (Mean age of the infants with BPD was 72.9 days vs 34.4 days for those without BPD.) Mechanical ventilation might affect lower esophageal sphincter

tone. As shown in Table 3, there was a trend toward less GER in infants receiving ventilation, although, due to the small sample size, the differences were not significant. Even the infants with BPD who were not receiving ventilation (Table 3), however, had less GER than did the infants without BPD (Table 2). A third possible explanation is the effect of increased strength and frequency of diaphragmatic contractions on lower esophageal sphincter tone. A recent study demonstrated that the normal oscillation of the lower esophageal sphincter pressure seen during respirations is due to diaphragmatic contractions, and lower esophageal sphincter pressure will increase with increased force of contraction of the diaphragm.²⁹ This effect can be explained anatomically by the way the crura fibers of the diaphragm

wrap around the lower esophageal sphincter, forming a "sling." As infants with BPD are usually tachypneic and/or hyperpneic, the increased diaphragmatic contractions may play a role in decreasing GER in these patients.

We found it impossible to obtain matched controls for the infants with BPD. Infants without BPD are rarely hospitalized for a prolonged period, and we could not obtain consent for the study of otherwise well infants who were already discharged. Therefore, we believed that the best (available) infants for comparison were those in our convalescent nursery who were having no problems other than apnea. However, this group of infants was similar to the infants with BPD in postconceptional age only and cannot be considered true controls.

The degree of GER found in this group of infants was surprising. All were asymptomatic except for apnea, and multichannel recordings did not demonstrate an association between GER and apnea. On follow-up, all of these infants were normal and growing well.

We believe that the diagnosis of "pathologic" GER can be excluded on clinical grounds. The amount of GER observed in these growing premature infants, therefore, either is normal or is related to some other factor.

Currently, there are no published normal data on GER in growing premature infants as measured by a pH probe in the upper esophagus. There is only one study of normal values for GER to the lower esophagus measured with a pH probe. Herbst et al¹¹ studied 14 hospitalized infants less than 6 weeks old and found that, although some of the neonates had mildly elevated scores, they did not differ significantly from those of older children. These infants were studied with the use of standard feeds and in all positions. The scores were based on measurements obtained more than 2 hours after feeding (this has been found to help identify symptomatic GER in older infants²⁶). These technical factors may explain the differences in GER found in growing premature infants in the two studies.

We studied our infants supine; they were fed dextrose water, and the data reported are those for the entire 6- to

12-hour study. We found that infant formulas will buffer gastric acid, raising the pH to levels above 4.0 for up to 2.5 hours after feeding. Thus, reflux of gastric contents during this period will not lower the esophageal pH. Sondheimer¹⁸ used a pH probe to monitor GER in infants who received alternating feedings of cows'-milk formula and apple juice (which is similar to dextrose water). She found more GER after a feeding of apple juice than after the cows'-milk formula. Although it is possible that an "acidic" feeding might exacerbate GER, Sondheimer thought (as we do) that this is unlikely. It is more likely that the apparent increase in GER (after ingestion of apple juice) resulted from the buffering effect of cows' milk. Because growing premature infants are fed every 2 to 4 hours, restricting observations to a period longer than 2

hours after a feeding will eliminate most of the day's data from the evaluation and much of the GER detectable in these infants. Methodologic differences could account for the discrepancy between our infants and those described by Herbst et al.¹¹ There is an urgent need for more studies of a growing neonatal population to establish normal values for GER in both the upper and lower esophagus.

There are obvious hazards in attempting to draw conclusions from this small descriptive study. The small sample size can lead to type I as well as type II errors.³⁰ However, the infrequent GER found in infants with BPD is perplexing. If GER contributes to the severity of the pulmonary disease in these infants, then aspiration after infrequent episodes of reflux may be sufficient to aggravate existing lung disease. Alter-

natively, GER may produce bronchospasm as a result of a vagal reflex from acid in the distal esophagus. This would not be recorded by a proximal pH probe. Monitoring proximal and distal esophageal pH simultaneously, together with transcutaneous P_{O_2} and PCO_2 , would document changes in respiratory status associated with GER in these infants. Such information might shed more light on the role of GER in chronic lung disease. Our data and those of Giuffre et al.¹³ suggest, however, that in selected cases (and by whatever mechanism) GER is a significant problem in BPD and that these infants may show a dramatic response to fundoplication.

We greatly appreciate the assistance of Kimberly Law and Janalee Baughman in the preparation of the manuscript.

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Postdelivery Head Bleeding in Hemophilic Neonates

Causes and Management

Morris Kletzel, MD; Connie H. Miller, PhD; David L. Becton, MD; William M. Chadduck, MD; Joseph M. Elser, MD

• During a 12-month period, four of the five infants with hemophilia known to have been born in Arkansas were examined for head bleeding. Three of the infants had had traumatic delivery, with use of low forceps in two and vacuum extraction in one. In the fourth patient, hemophilia was prenatally diagnosed, and vaginal delivery resulted in cephalohematoma. Diagnosis was delayed in three patients, including one with a family history of hemophilia. Central nervous system bleeding may be more common in hemophilic neonates than has been presumed. Pregnancy management should include consideration of family history of bleeding disorders and carrier testing in appropriate cases. In confirmed carriers, prenatal diagnosis is justified to allow choice of the least traumatic delivery method. Any term neonate with intracranial hemorrhage should be treated as being possibly hemophilic until proved otherwise.

(AJDC. 1989;143:1107-1110)

Hemophilia is an X-linked coagulation disorder due to deficiency of factor VIII or factor IX, occurring in moderate or severe form in 1 of 8000 male births.¹ Two thirds of hemophiliacs are born to women with a family history of the disorder.² Availability of restriction fragment length polymorphism analysis has improved the accuracy of carrier detection and the safety of prenatal diagnosis, which can now be performed by chorionic villus sampling or amniocentesis rather than by fetal blood sampling in the majority of cases.³ Up to one half of hemophilia carriers elect prenatal di-

agnosis,² but termination of pregnancy is unacceptable to many.^{2,4} Therefore, delivery of an infant known to be at risk is not infrequent. Although intracranial hemorrhage is a leading cause of death in hemophiliacs, its occurrence in the neonate has been considered rare, with an incidence of 1% to 4%.⁵⁻⁷ Modification of delivery methods for potentially affected infants has not usually been recommended.^{8,9}

During a 12-month period, four of the five hemophiliacs known to have been born in the state of Arkansas were examined with signs of head bleeding, with one fatality. We describe these patients, with recommendations for appropriate management of at-risk pregnancies and the bleeding newborn.

PATIENT REPORTS

PATIENT 1.—A 4-day-old white boy had been born to a 28-year-old, gravida 1 woman at term by spontaneous vaginal delivery with the use of low forceps. He was circumcised on day 2, developing bleeding that was stopped with two sutures. Three days after discharge from the nursery, he was taken to the local emergency department with apneic spells. An evaluation to rule out sepsis was performed, and he was admitted to the local hospital and started on a regimen of broad-spectrum antibiotics. Because of a drop in hematocrit and oozing from venipuncture sites, he was given 10 mL/kg of fresh-frozen plasma (FFP) and packed red blood cells. A computed tomographic (CT) scan and ultrasound of the head revealed a large subdural hematoma, intracerebral hemorrhage, and marked cerebral edema (Fig 1). After administration of FFP, the patient's factor VIII level was 24%. He was then given cryoprecipitate. He became apneic and was intubated and transferred to Arkansas Children's Hospital, Little Rock.

On the patient's arrival, activated partial thromboplastin time (PTT) was 26.2 seconds (normal, 21.0 to 32.0 seconds), prothrombin time was 11.7 seconds (control, 12.0 sec-

onds), fibrin degradation products and platelet counts were normal, and no evidence of fragmented red blood cells was seen on smear. After neurosurgical evaluation, 5 mL of blood was removed from the posterior fossa. Cryoprecipitate treatment was continued, and normal results of coagulation studies were maintained. While receiving mechanical ventilation, the patient developed inappropriate secretion of antidiuretic hormone syndrome. A second CT scan revealed massive cerebral edema with complete loss of gray and white matter interface. An ultrasound scan of the head showed reverse flow into the cranium. Because of the devastating central nervous system injury, he died at 7 days of age.

Although there was no family history of coagulation disorders, the mother had low factor VIII levels on two occasions. Examination of six family members showed no other evidence of hemophilia or von Willebrand's disease. The mother's test results on two occasions indicated that she was a carrier of hemophilia (Table 1), confirming the diagnosis in the patient. The maternal grandmother's test results were inconclusive. DNA analysis was not attempted.

In a subsequent pregnancy, the parents elected prenatal diagnosis and were found to have a female fetus.

PATIENT 2.—A 4-day-old white boy had been born vaginally with low forceps at term to a gravida 1 mother. Membranes had ruptured 12 hours before delivery. The patient underwent circumcision on day 2 without complication. Twenty-four hours later, he returned to the local physician with persistent bleeding, and a suture was placed at the site of circumcision. At that time he was vomiting, for which his formula was changed.

Twenty-four hours later, the patient returned with persistent vomiting and lethargy. An evaluation to rule out sepsis was performed, and he was started on a regimen of ampicillin sodium and ceftriaxone sodium (Rocephin). His total bilirubin level was 513 $\mu\text{mol/L}$. He was then transferred to a regional hospital where he required intubation. His pupils were pinpoint, with a tense fontanelle. An ultrasound scan of the head showed evi-

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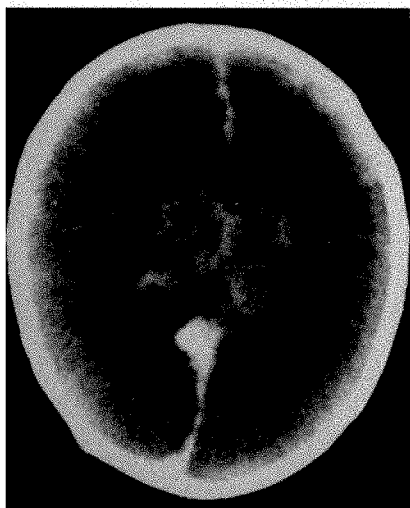


Fig 1.—Computed tomographic scan of patient 1, without contrast, showing a posterior ossa interhemispheric subdural hematoma with subarachnoid hemorrhage and massive cerebral edema with more mass effect on the right than the left, with a midline shift.



Fig 2.—Computed tomographic scan of patient 2 showing a large hemorrhage involving the third ventricle with obstructive hydrocephalus. A small hemorrhage can also be detected in the lateral ventricle.

Table 1.—Hemophilia Carrier Test Results in Family of Patient 1

Relative	Factor VIII, %	vWF Antigen, %	Ratio of VIII/vWF
Mother	43	69	0.62
	24	55	0.44
Maternal grandmother	142	192	0.74
Maternal aunt	159	161	0.99
Normal range	50-200	50-200	>0.73 ¹¹

ence of an intracranial hemorrhage. Laboratory evaluation gave the following values: hemoglobin, 124 g/L; hematocrit, 0.36; platelet count, $354 \times 10^9/L$; glucose, 33.8 mmol/L; total bilirubin, 393.3 $\mu\text{mol/L}$; prothrombin time, 12 seconds (control, 12 seconds); PTT, 31 seconds (normal, 21.0 to 32.0 seconds); and factor VIII, 6%. He was given cryoprecipitate and transferred to our institution.

On the patient's arrival, a CT scan of the head was performed, revealing a large hemorrhage in the third ventricle, with obstructive hydrocephalus and a small hemorrhage in the lateral ventricle (Fig 2). Replacement therapy with factor VIII concentrate (Monolate, Armour Pharmaceutical Co, Tarrytown, NY) was started. The patient developed progressive hydrocephalus, and a ventriculoperitoneal shunt was placed on day 21. The patient continued to receive replacement therapy for 14 days, after which he was discharged.

The family history is unknown because the mother was adopted. After discharge, no bleeding problems occurred, and the result of factor VIII assay without replacement ther-

apy was less than 1%. Results of a neurodevelopmental assessment 3 months later were normal.

PATIENT 3.—A 2-day-old black boy had been born vaginally with vacuum extraction at 41 weeks of gestational age to a 23-year-old, gravida 2 mother. He was circumcised immediately after birth. On day 2 he was noted to have an increase in head circumference and pallor. Laboratory evaluation at that time revealed a hematocrit of 0.13, platelet count of $190 \times 10^9/L$, prothrombin time of 14.5 seconds, and PTT of 95 seconds. His mother was noted to have a family history of hemophilia.

The child immediately received FFP, packed red blood cells, and phytonadione and was transferred to our institution, where his head circumference was found to be at the 90th percentile, with a bulging fontanelle and a left cephalohematoma. A CT scan and ultrasound scan of the head failed to show an intracranial hemorrhage; all bleeding was localized in the subgaleal compartment. Laboratory evaluation on admission revealed a hematocrit of 0.19, prothrombin time of 12

seconds (control, 12 seconds), PTT of 35.2 seconds, factor VIII level of 29%, and factor IX level of 80%, after he had received FFP. He was given replacement therapy with factor VIII concentrate for an additional 7 days and showed a marked recovery. Factor VIII level without replacement was less than 1%. He had no neurologic sequelae.

The pedigree obtained by history is shown in Fig 3. A 3-year-old brother was unaffected.

PATIENT 4.—A 2-day-old white boy had been born at term by spontaneous vaginal delivery to a 26-year-old, gravida 3 mother, without complications during labor or delivery. Because she had a 2-year-old son with severe factor IX deficiency, the mother underwent prenatal diagnosis. DNA analysis of cells obtain amniocentesis indicated that this fetus also had factor IX deficiency.

At 8 hours of age, the infant was noted to have a progressively enlarging cephalohematoma and increasing lethargy. A CT scan and ultrasound scan failed to show intracranial hemorrhage. The diagnosis of factor IX deficiency was confirmed. The child received FFP and recovered from the initial episode. While receiving replacement therapy, he was circumcised without complications. On follow-up no sequelae were found.

COMMENT

Intracranial hemorrhage in the neonate with hemophilia is considered to be rare. A retrospective study⁶ of 71 patients with central nervous system bleeding among 2500 hemophiliacs found only 3 in the newborn period. More recently, review of records on 150 hemophiliacs found intracranial bleeding to be the initial sign in 8 patients, 5 of whom were less than 1 week of age.⁷ Our experience leads us to suggest that the incidence may be higher, since such retrospective studies include only those infants who survived until a diagnosis was made.

Among the 18 000 male births annually in Arkansas, 2.25 hemophilic newborns per year would be expected.¹ During a recent 12-month period, five hemophilic infants were known to have been born in the state. Arkansas Children's Hospital is the major referral hospital for children in the state and has the only hemophilia treatment program. Most hemophilic infants are therefore seen at our institution, and ascertainment is likely to be nearly complete. Four of the five infants with hemophilia had signs and symptoms of

Table 2.—Summary of Cases

Case No.	Factor Deficiency	Family History	Age at Diagnosis of Hemophilia, d	Type of Delivery	Presenting Symptoms	Outcome
1	VIII	Negative	4	Vaginal, forceps	Apneic spells	Dead
2	VIII	Negative	4½	Vaginal, forceps	Lethargy, vomiting	Alive, VP shunt
3	VIII	Cousin with hemophilia	2	Vaginal, vacuum	Increase in head circumference	Alive, no sequelae
4	IX	Brother with hemophilia	2	Vaginal	Increase in head circumference	Alive no sequelae

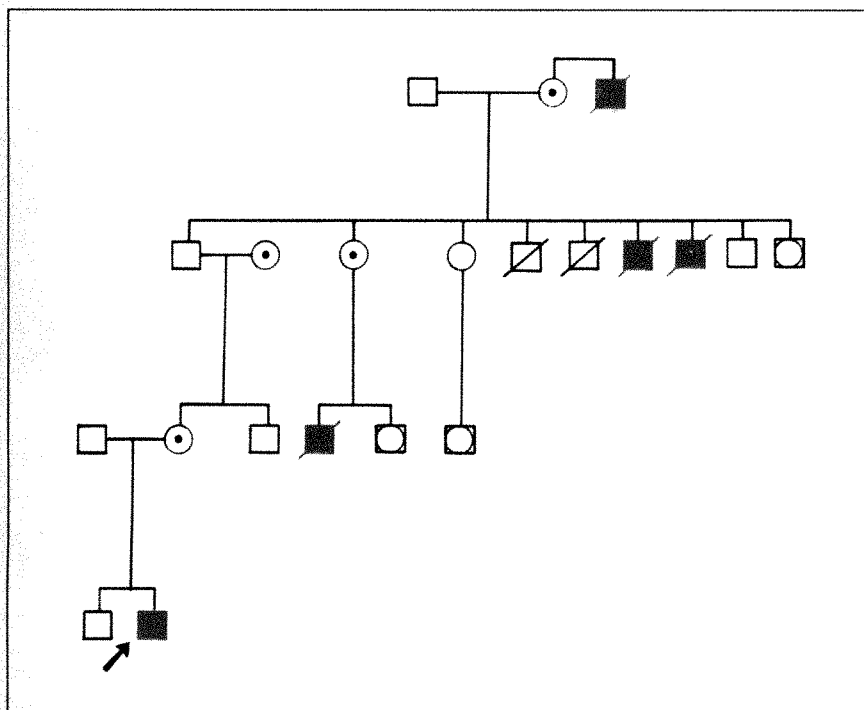


Fig 3.—Pedigree of patient 3 (arrow). Closed squares indicate patients with classic hemophilia; open circles with dot in center, hemophilia carrier.

head bleeding. The details of diagnosis, delivery, and outcome are summarized in Table 2. Two infants had intracranial hemorrhage, and one of those died. The common feature in three of the cases is traumatic delivery. Two of the patients were delivered with use of low forceps and one with vacuum extraction. For delivery of the fourth patient, whose condition had been diagnosed prenatally, use of cesarean section had been planned if difficulties arose, to avoid excessive head trauma. Vaginal delivery without intervention resulted in cephalohematoma. The association of intracranial bleeding with traumatic delivery was documented in three of the five newborns with intracranial hemorrhage described by Bray and Luban¹¹ and one of the five described by Yoffe and Bu-

chanan.⁷ Hemophilic infants are clearly at risk for head trauma under some delivery conditions.

Delay in recognition of the diagnosis undoubtedly contributed to morbidity and mortality in our patients. It is likely that the diagnosis could have been made 24 to 48 hours earlier if the index of suspicion had been higher. In the two patients without family history of hemophilia, sepsis was suspected initially; histories of bleeding from circumcision and traumatic delivery were ignored. As would be expected, appropriate treatment was initiated more rapidly in those infants with hemophilic relatives. However, patient 3, an at-risk infant, was not tested before circumcision and discharge from the local hospital. The long lag time between trauma and ap-

pearance of symptoms is typical of central nervous system bleeding in hemophiliacs.⁵ In these patients low hematocrit and/or prolonged PTT led to the performance of coagulation factor assays and appropriate replacement therapy before transfer to the tertiary care center. In no instance was neurosurgery performed without diagnosis, as has previously been reported.¹¹ Use of cryoprecipitate for treatment of factor VIII-deficient children was standard care in Arkansas until 1987 due to the low incidence of human immunodeficiency virus and hepatitis B infection.¹²

Intracranial hemorrhage is a common occurrence in the premature newborn. In the term infant, however, it should alert the pediatrician or neonatologist to the possible diagnosis of hemophilia. It has been suggested that full-term newborn boys with intracranial hemorrhage be considered hemophilic until proved otherwise.^{7,11}

From our experience and that of others, we draw the following conclusions:

1. Inquiry about personal and family history of bleeding disorders is crucial to appropriate delivery management for every pregnant woman and, since two thirds of hemophiliacs are born to women with family histories of the disorder,² will reveal the risk in the majority of cases.

2. When family history is present, pregnant potential carriers should be tested by coagulation studies or, preferably, DNA analysis to aid in management.

3. In women who are carriers of hemophilia, prenatal diagnosis by amniocentesis and DNA analysis, when possible, appears justified for management of a safe delivery. Risks of the procedure and various delivery options should be discussed with the patient.

4. If a bleeding disorder is suspected or is diagnosed prenatally, the least traumatic delivery method should be se-

lected to minimize the risk of intracranial hemorrhage, and a pediatrician or neonatologist familiar with hemophilia treatment should attend the birth. If presence of a bleeding disorder can be ruled out, the woman may be spared an unnecessary cesarean section.

5. Diagnosis of intracranial hemorrhage by ultrasound or CT scan in a term newborn should prompt intervention with replacement therapy with FFP until the diagnosis is known, to minimize the damage to the central nervous system. Specific factor replacement

should then follow with the appropriate concentrate in its most virus-free form.

We wish to thank Mary Jo Whaley and Jacquelyn Ford for assistance in collecting patient data and Flora Hawks for artwork.

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CORRECTION

Incorrect Phrasing.—In the letter entitled "Interactions of Alcohol and Nutrition," published in the May issue of *AJDC* (1989;143:519), errors appeared in two places. In the second paragraph, second sentence, where the text reads "...for example, as well as the increased urinary excretion, . . ." the two words "for example," should be removed. In the fourth sentence of the same paragraph, where the text reads "... that this effect could explain increased . . .," the word "explain" should be replaced with "reflect."

Hypophosphatemia in the Nutritional Recovery Syndrome

Adam G. Mezoff, MD; David A. Gremse, MD; Michael K. Farrell, MD

• We studied the incidence of hypophosphatemia in patients during the nutritional recovery syndrome. The charts of 150 patients receiving a complete nutritional assessment for 18 months were reviewed; 45 met established nutritional risk criteria. Only 9 of these 45 had serial phosphorus values measured during nutritional repletion, and 5 of these 9 patients had hypophosphatemia (phosphorus levels <0.97 mmol/L). Anthropometric measurements of arm circumference and arm muscle circumference were less than the fifth percentile in all patients developing hypophosphatemia. We concluded that hypophosphatemia is an underrecognized complication of nutritional repletion and that anthropometric measurements may be predictive of patients at risk. All patients with significant malnutrition should be evaluated for this complication of refeeding.

(AJDC. 1989;143:1111-1112)

Hypophosphatemia is a significant complication of several conditions, including alcoholism, diabetic ketoacidosis, parenteral nutrition, severe respiratory alkalosis, chronic antacid therapy, and the recovery phase after severe burns. A significant cause of hypophosphatemia in children is the nutritional recovery syndrome, defined as a constellation of events occurring during the refeeding of significantly protein energy malnourished patients.¹ Prolonged hypophosphatemia may result in dysfunction of several different organ systems including hematologic, neurologic, and nephrologic.

We therefore sought to determine the incidence of hypophosphatemia in malnourished children as a complication of nutritional rehabilitation, to identify

clinical or biochemical risk factors for the development of hypophosphatemia in these children, and to review the major complications and treatment of this potentially fatal but eminently treatable condition.

PATIENTS AND METHODS

The medical records of all inpatients who underwent formal nutritional assessment at our institution from January 1, 1987, to June 1, 1988, were reviewed. In all patients, weight, length, and head circumference were measured according to the methods described by Jelliffe.² Weight/length index as well as ideal weight for length were calculated. Midarm muscle circumference, arm muscle area, midarm circumference, triceps skin-fold thickness, and subscapular skin-fold thickness were measured and used to estimate somatic protein stores and body fat composition.³⁻⁸ Visceral protein stores were estimated by retinol-binding protein, prealbumin, transferrin, and albumin determinations.^{9,10} Nutritional requirements were estimated by oxygen consumption testing.^{11,12}

We defined a malnourished patient as one whose nutritional assessment demonstrated at least one of the previously established nutritional risk criteria, and had a history and clinical findings compatible with protein energy malnutrition. These criteria included the following: height and weight less than the fifth percentile; muscle arm circumference less than 5%; albumin levels of less than 35 g/L; prealbumin and retinol-binding protein less than normal for age; weight/height index less than 90%; arm circumference and triceps skin-fold less than the fifth percentile; transferrin levels less than 2 g/L; and total lymphocyte count less than 1.5×10^9 /L.

Refeeding was defined as providing at least 75% of the patient's estimated energy needs for growth with demonstrable weight gain. Subjects were included in this study if serum phosphorus concentration was measured before refeeding, after the onset of refeeding, and serially thereafter. Hypophosphatemia was defined as a serum concentration of less than 0.97 mmol/L. Patients with underlying conditions that would interfere with phosphorus metabolism, absorption, or excretion were excluded. Patients whose serum phosphorus values did not return to normal after adequate supplementation were also excluded.

RESULTS

The medical records of 150 inpatients for whom adequate nutritional assessments were performed were reviewed. Their ages ranged from 6 months to 19 years. Of these 150 patients, 45 were malnourished by nutritional risk criteria and had no underlying condition that would affect phosphorus metabolism. The diagnoses of these patients included the following: failure to thrive ($n=12$), mental retardation/cerebral palsy ($n=9$), anorexia nervosa ($n=7$), juvenile rheumatoid arthritis ($n=3$), Crohn's disease ($n=3$), biliary atresia ($n=2$), cyanotic congenital heart disease ($n=2$), teratoma ($n=1$), apnea ($n=1$), tricyclic ingestion ($n=1$), scleroderma ($n=1$), meningitis ($n=1$), Niemann-Pick disease ($n=1$), and gunshot wound/pelvic osteomyelitis ($n=1$). Three of the patients with mental retardation/cerebral palsy, 1 of the patients with anorexia nervosa, and the patient with gunshot wound/pelvic osteomyelitis all were hypophosphatemic. The serum phosphorus concentration was measured in only 9 (20%) of these 45 patients during the initial part of their nutritional resuscitation.

Six episodes of hypophosphatemia occurred in five of these nine patients during renourishment. Two hypophosphatemic episodes resulted in serum phosphorus concentrations less than 0.32 mmol/L, two with concentrations between 0.32 and 0.64 mmol/L, and two episodes with concentrations between 0.64 and 0.97 mmol/L. The serum phosphorus concentration decreased in two patients within 24 hours of refeeding, and in all patients within 72 hours.

We analyzed all measurements and found that arm circumference and arm muscle circumference measurements were the nutritional risk factors predictive for all episodes of hypophosphatemia. Weight/height index and triceps skin-fold thickness met nutritional risk criteria in four of five patients with hypophosphatemia and are shown in the following tabulation:

Accepted for publication March 27, 1989.

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Predictive Nutritional Measurements	No. of Patients With Abnormality/ Total No. of Hypophosphatemic Patients
Arm muscle circumference <5%	5/5
Arm circumference <5%	5/5
Weight/height index	4/5
Triceps skin-fold thickness <5%	4/5
Hypoalbuminemia <3.5 mg/dL	2/5

Hypophosphatemia was accompanied by a decreased concentration of visceral proteins (albumin) in only two of six occurrences. No obvious clinical complications of hypophosphatemia were observed in nine patients, and our review did not suggest signs or unexplained symptoms that might be due to phosphorus depletion.

COMMENT

Hypophosphatemia is a known but infrequently reported complication of nutritional rehabilitation. Our data suggested that hypophosphatemia may occur more frequently in malnourished children during nutritional rehabilitation than previously appreciated and that there is a general unawareness of this problem. Indeed, 36 of 45 malnourished patients in our study were not assessed for hypophosphatemia. The clinical importance of hypophosphatemia in our patients is unknown because timely institution of replacement therapy prevents symptoms; however, significant side effects of hypophosphatemia have been previously reported, and usually after 48 to 72 hours.¹²⁻¹⁸ Symptomatic hypophosphatemia often occurs with serum phosphorus concentrations of less than 0.32 mmol/L, affecting the hematologic, musculoskeletal, and central nervous systems.

In animals, hypophosphatemia causes decreased leukocyte adenosine triphosphate concentrations, thus depressing chemotaxis, phagocytosis, and bacterial killing, and resulting in an increased incidence of infection.¹⁹ Severe hypophosphatemia blocks red blood cell glycolysis by inhibiting the glyceraldehyde-3-phosphatase dehydrogenase reaction,¹⁸ producing a decrease in adenosine triphosphate production. Decreased adenosine triphosphate production causes a hemolytic

anemia that resolves following phosphorus repletion.¹⁴ Hypophosphatemia also impedes oxygen delivery to peripheral tissues by decreasing the production of 2-3-diphosphoglycerate, thereby increasing the affinity of hemoglobin for oxygen. Finally, platelet dysfunction with low serum phosphorus concentrations has been reported,¹⁵ including reduced adenosine triphosphate-dependent clot retraction.

Rhabdomyolysis has been observed in severe hypophosphatemia. Elevation of creatinine phosphokinase concentrations and myoglobinuria accompany acute renal failure.¹⁶ This tends to be self-limiting as phosphorus is released with the lysis of muscle cells.

Central nervous system dysfunction may be manifest by symptoms compatible with a metabolic encephalopathy, including irritability, apprehension, muscular weakness, paresthesia, dysarthric obtundation, seizures, and even coma.¹⁷ Other disturbances associated with severe hypophosphatemia include reversible cardiomyopathy, glucose intolerance, and nonspecific gastrointestinal complaints, such as anorexia, nausea, and vomiting.¹⁷

The anthropometric measurement of arm circumference and arm muscle circumference were the most predictive measures in our series of patients at risk for hypophosphatemia. In all six episodes of hypophosphatemia these were less than 5%. Laboratory measurements of visceral proteins were abnormal in only two of six episodes, namely, a low serum albumin level, which may reflect the body's ability to selectively break down less essential protein stores. All patients developing hypophosphatemia with renourishment did so within 72 hours, and most within 24 to 48 hours.

All patients who became hypophosphatemic were treated with supplemental phosphorus. Patients with minimal to moderate hypophosphatemia (concentrations higher than 0.32 mmol/L but lower than 0.97 mmol/L) were treated orally, with doses between 25 and 50 mg/kg each day (1.4 to 2.8 mEq/kg each day or 0.8 to 1.6 mmol/kg each day) of phosphorus divided four times daily. Treatment of profound hypophosphatemia (concentrations less than 0.32 mmol/L) was generally accom-

plished intravenously. Guidelines for intravenous supplementation have been published previously.¹⁸ Parenteral phosphorus should be initiated at a dose of 0.08 mmol/kg in short-term and uncomplicated cases, and 0.16 mmol/kg in a prolonged case with multiple causes (at pH 7.4, 3.1 mg/dL of phosphorus, 1 mmol/L or 1.8 mEq/L).

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NEONATOLOGIST — The Department of Pediatrics, William Beaumont Hospital is seeking a fifth full-time, academically-oriented neonatologist to join our Division of Newborn Medicine. The position involves clinical care, teaching and research. We are interested in recruiting somebody with demonstrated capability and interest in clinical and/or basic research, as well as proficiency in teaching residents. Interested individuals should submit their CV to: Daniel Batton, MD, Chief, Division of Newborn Medicine; or M. Jeffrey Maisels, MD, Chairman, Department of Pediatrics, William Beaumont Hospital, 3601 West Thirteen Mile Road, Royal Oak, MI 48072.

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Huntington Memorial Hospital of Pasadena, California, a major affiliate of the University of Southern California School of Medicine, is seeking to hire four board eligible/certified pediatricians to cover its 34-bed pediatric floor. These four house-based pediatricians (HBPs) will provide in-house coverage that traditionally would have been provided by pediatric interns or residents.

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NEW YORK, NEONATOLOGIST—Department of pediatrics, State University of New York at Buffalo/Children's Hospital is seeking faculty member to join eight-member division of neonatology. Assistant or associate professor level. BC in pediatrics, BC/BE in neonatology. Division conducts NIH-sponsored laboratory research on perinatal pulmonary and circulatory physiology and clinical research in pulmonary physiology, immunology and gastroenterology, including five years experience with surfactant therapy. CV to: Frederick C. Monn, MD, Chief, Division of Neonatology, Children's Hospital, 219 Bryant Street, Buffalo, NY 14222. Affirmative action/equal opportunity employers.

THE DEPARTMENT OF PEDIATRICS at William Beaumont Hospital is seeking a qualified pediatrician for the position of Director, Division of Pediatric Infectious Disease. William Beaumont Hospital is a 934-bed general hospital located thirteen miles north of Detroit in Royal Oak, Michigan. We have 60 general pediatric beds, a 30-bed NICU and 6,000 deliveries annually. Our department has a staff of 120 pediatricians and 20 full-time pediatric subspecialists. There are some 4,000 admissions annually to our general pediatric floor and 20,000 pediatric visits to the emergency center and outpatient clinics. We are a teaching hospital with independent residency programs in pediatrics and medicine-pediatrics, affiliated with the University of Michigan and Wayne State University. Interested candidates should call or submit their curriculum vitae to: M. Jeffrey Maisels, MD, Chairman, Department of Pediatrics, William Beaumont Hospital, 3601 West Thirteen Mile Road, Royal Oak, MI 48072. (313) 551-0412.

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... on the consumer promotion of infant formula.

There is a development that undermines your control over the infant's diet and health, and that undermines breastfeeding—the advertisement of formulas directly to the mother through TV, magazines and mail.

On June 1, the President of the American Academy of Pediatrics sent a letter to all Fellows of the Academy reaffirming its stance against consumer advertising, and expressing concern that other formula companies might follow Nestlé/Carnation.

This concern was justified. On June 15, it was announced at a press conference that Mead Johnson/Bristol-Myers will be producing an infant formula to be sold and marketed under the Gerber label. Part of the program is a multimillion-dollar budget for advertising the formula directly to mothers via TV and print.

Speaking at the press conference, Gerber Products Division President Robert L. Johnston, Jr., said that Gerber was entering the market because it had, "identified significant changes in usage that convinced us the timing was right. . . ."

"First," he said, "there is a rapid decline in breast-feeding after mothers leave the hospital." And, "... parent decision regarding baby formula brand selection has grown. . . ."

The irony is inescapable and appalling. In other words, because breastfeeding is declining, more infant formulas should be promoted to the mother. In other words, because some mothers are making feeding decisions on their own, even more mothers should follow suit.

When Nestlé/Carnation entered the marketplace and, again, when Mead Johnson/Bristol-Myers joined with Gerber, we reexamined the Ross philosophy of promoting SIMILAC® Infant Formulas. The result of our deliberations was an even deeper resolve to support the doctor/patient relationship.

Our philosophy remains unchanged. Ross Laboratories has no plans to resort to direct consumer advertising for SIMILAC and our other infant formula products.

We will continue as an ally of health care professionals by supporting your prerogative to prescribe and recommend products as training and experience dictate.

We stand behind you.

Richard W. Gast



Continued from p 1117.

EDUCATIONAL INTERVENTIONS

1173 Management of Diabetes in Pediatric Resident Continuity Clinics

Kathleen K. Kronz, Roberta Ann Hibbard, MD;
David G. Marrero, PhD, Indianapolis, Ind;
Gary M. Ingersoll, PhD, Bloomington, Ind;
Naomi S. Fineberg, PhD, Michael P. Golden, MD, Indianapolis, Ind

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1181 Reye's Syndrome

Marie Gauthier, MD; Joanne Guay, MD;
Jacques Lacroix, MD; Anne Lortie, MD, Montreal, Canada

1186 Neurologic Status and Intracranial Hemorrhage in Very-Low-Birth-Weight Preterm Infants

Lisa M. Ford, MD; Jean Steichen, MD; Paula A. Steichen Asch, PhD;
Diane Babcock, MD; M. H. Fogelson, MD, Cincinnati, Ohio

1191 Hypophosphatemia in Breast-fed Low-Birth-Weight Infants Following Initial Hospital Discharge

Robert T. Hall, MD, Robin E. Wheeler, MS, RD, Kansas City, Mo;
Michael B. Montalto, MS, John D. Benson, PhD, Columbus, Ohio

1196 Nasal Intermittent Positive-Pressure Ventilation Offers No Advantages Over Nasal Continuous Positive Airway Pressure in Apnea of Prematurity

C. Anthony Ryan, MB, MRCP(Ire), MRCP(UK), FRCPC;
Neil N. Finer, MD, FRCPC;
Katherine L. Peters, RN, BScN, MN, Edmonton, Canada

1199 Pertussis in Neonates

Celia D. C. Christie, MB,BS, DM Peds,
Robert S. Baltimore, MD, New Haven, Conn

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1207 Radiological Cases of the Month

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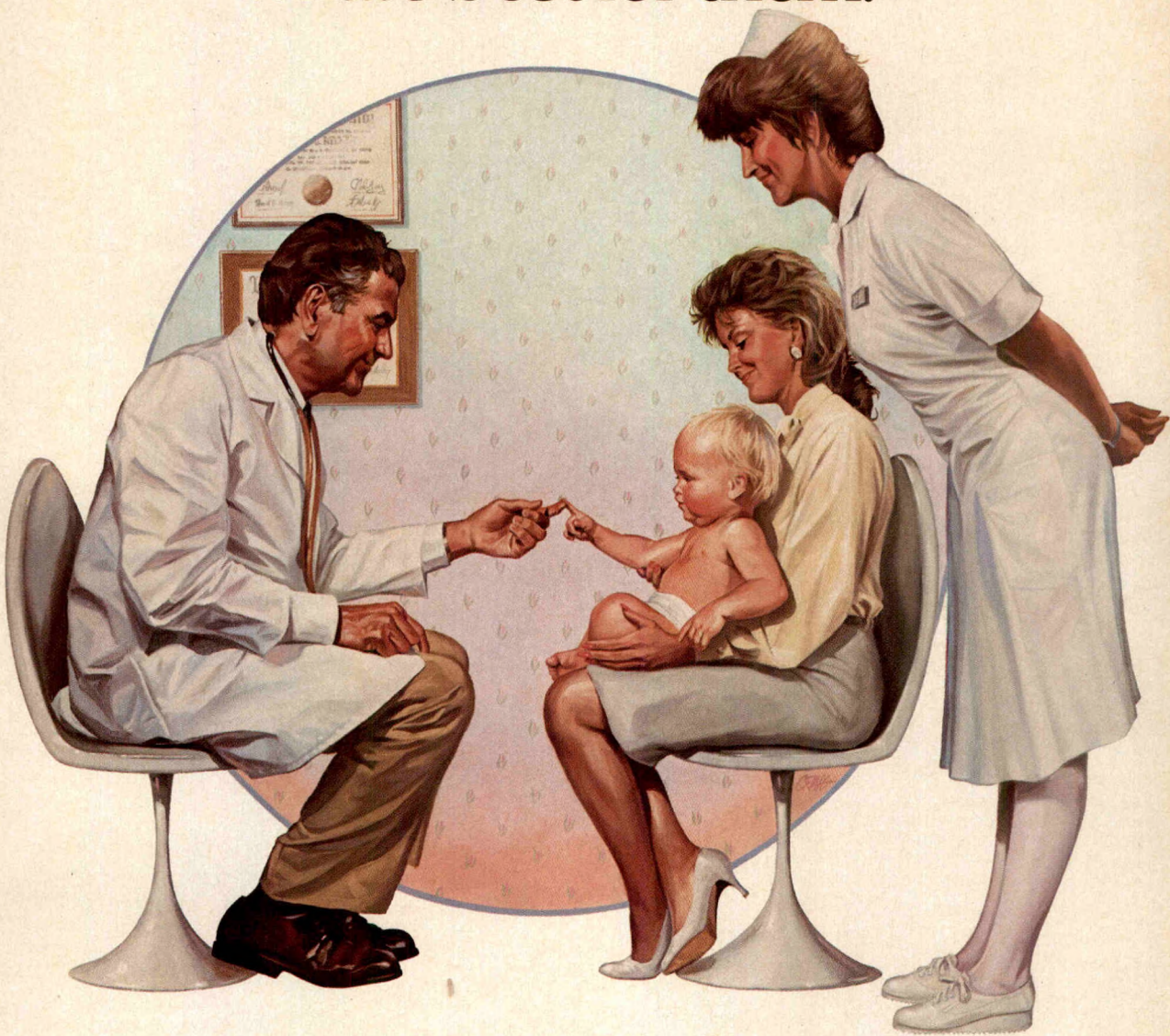
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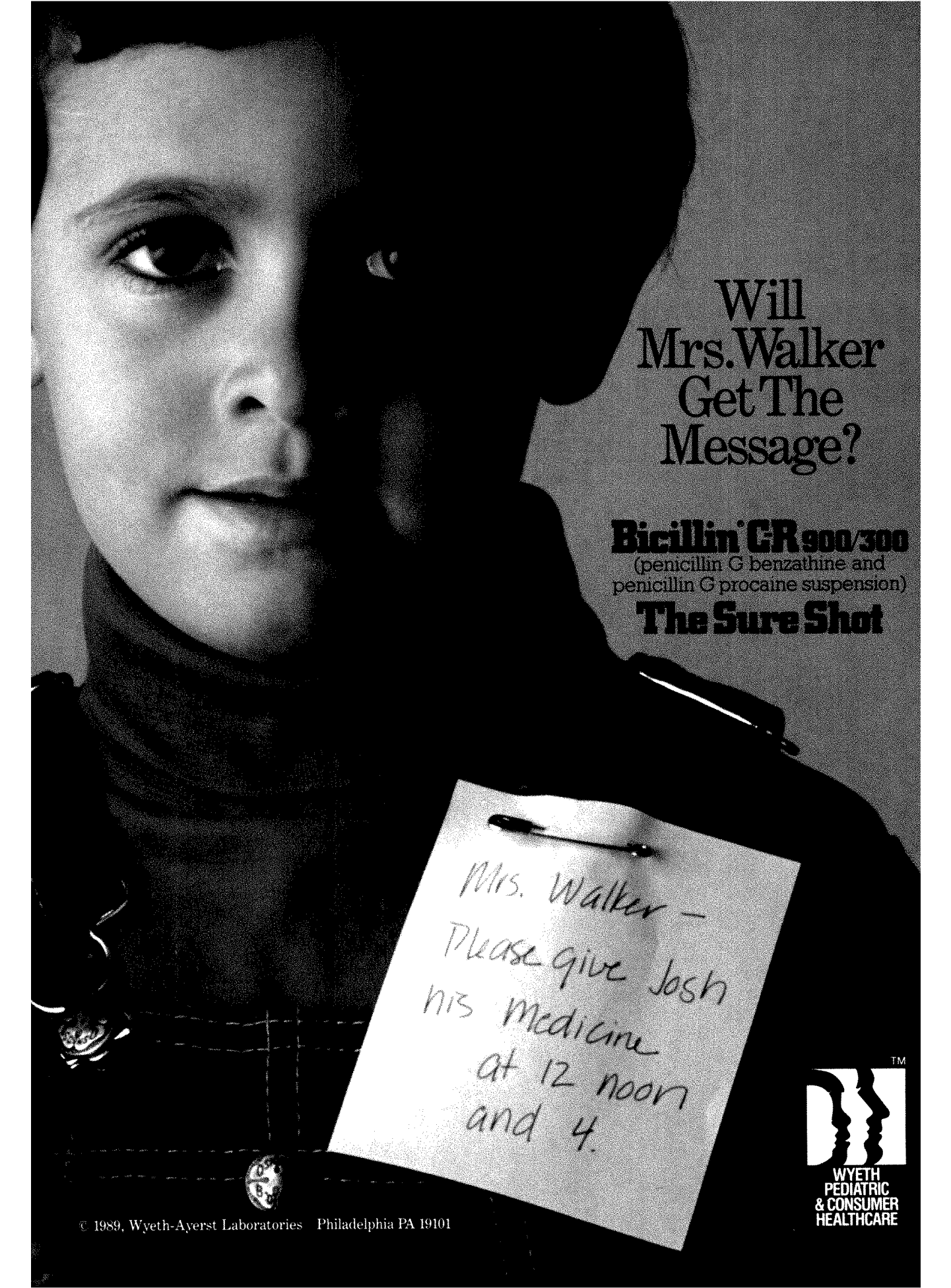
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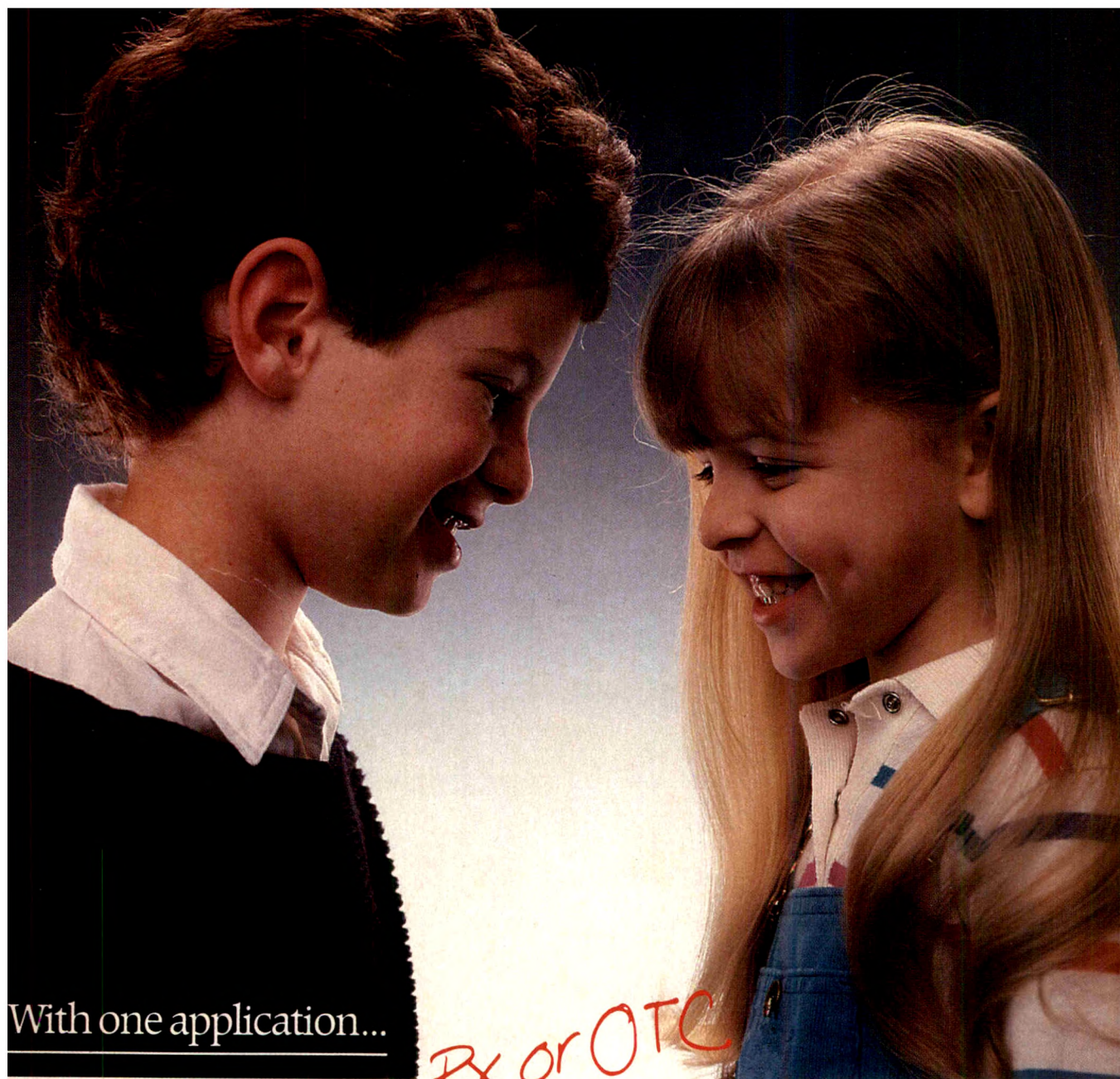
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INDICATIONS AND USAGE: Nix is indicated for the single-application treatment of infestation with *Pediculus humanus var. capitis* (the head louse) and its nits (eggs). Retreatment for recurrences is required in less than 1% of patients since the ovicidal activity may be supplemented by residual persistence in the hair. If live lice are observed after at least seven days following the initial application, a second application can be given.

CONTRAINDICATIONS: Nix is contraindicated in patients with known hypersensitivity to any of its components, to any synthetic pyrethroid or pyrethrin, or to chrysanthemums.

WARNING: If hypersensitivity to Nix occurs, discontinue use.

PRECAUTIONS:

General: Head lice infestation is often accompanied by pruritus, erythema, and edema. Treatment with Nix may temporarily exacerbate these conditions.

Information for Patients: Patients with head lice should be advised that itching, redness, or swelling of the scalp may occur after application of Nix. If irritation persists, they should consult their physician. Nix is not irritating to the eyes; however, patients should be advised to avoid contact with eyes during application and to flush with water immediately if Nix gets in the eyes. In order to prevent accidental ingestion by children, the remaining contents of Nix should be discarded after use.

Combing of nits following treatment with Nix is not necessary for effective treatment. However, patients may do so for cosmetic or other reasons. The nits are easily combed from the hair treated with Nix after drying.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Six carcinogenicity bioassays were evaluated with permethrin, three each in rats and mice. No tumorigenicity was seen in the rat studies. However, species-specific increases in pulmonary adenomas, a common benign tumor of mice of high spontaneous background incidence, were seen in the three mouse studies. In one of these studies there was an increased incidence of pulmonary alveolar-cell carcinomas and benign liver adenomas only in female mice when permethrin was given in their food at a concentration of 5000 ppm. Mutagenicity assays, which give useful correlative data for interpreting results from carcinogenicity bioassays in rodents, were negative. Permethrin showed no evidence of mutagenic potential in a battery of *in vitro* and *in vivo* genetic toxicity studies. Permethrin did not have any adverse effect on reproductive function at a dose of 180 mg/kg/day orally in a three-generation rat study.

Pregnancy: Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits (200-400 mg/kg/day orally) and have revealed no evidence of impaired fertility or harm to the fetus due to permethrin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the evidence for tumorigenic potential of permethrin in animal studies, consideration should be given to discontinuing nursing temporarily or withholding the drug while the mother is nursing.

Pediatric Use: Nix is safe and effective in children two years of age and older. Safety and effectiveness in children less than two years of age have not been established.

ADVERSE REACTIONS: The most frequent adverse reaction to Nix is pruritus. This is usually a consequence of head lice infestation itself, but may be temporarily aggravated following treatment with Nix. 5.9% of patients in clinical studies experienced mild temporary itching; 3.4% experienced mild transient burning/stinging, tingling, numbness, or scalp discomfort; and 2.1% experienced mild transient erythema, edema, or rash of the scalp.

DOSAGE AND ADMINISTRATION:

Adults and Children: Nix is intended for use after the hair has been washed with shampoo, rinsed with water and towel dried. Apply a sufficient volume of Nix to saturate the hair and scalp (especially behind the ears and on nape of the neck). Nix should remain on the hair for 10 minutes before being rinsed off with water. A single treatment is sufficient to eliminate head lice infestation. Combing of nits is not required for therapeutic efficacy, but may be done for cosmetic reasons or to meet school "no nit" policies. A nit comb is provided.

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HOW SUPPLIED: Nix (Permethrin) 1% (wt./wt.) Creme Rinse is supplied in plastic squeeze bottles that contain 2 fl. oz. weighing 56 g. (NDC-0081-0780-81)

Store at 15°-25°C (59°-77°F).

References:

1. Brandenburg K, Deinard AS, DiNapoli J, et al: 1% permethrin cream rinse vs 1% lindane shampoo in treating pediculosis capitis. *Am J Dis Child* 1986; 140:894-896.
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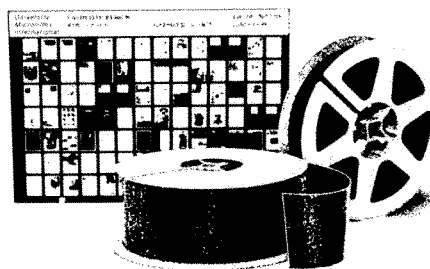
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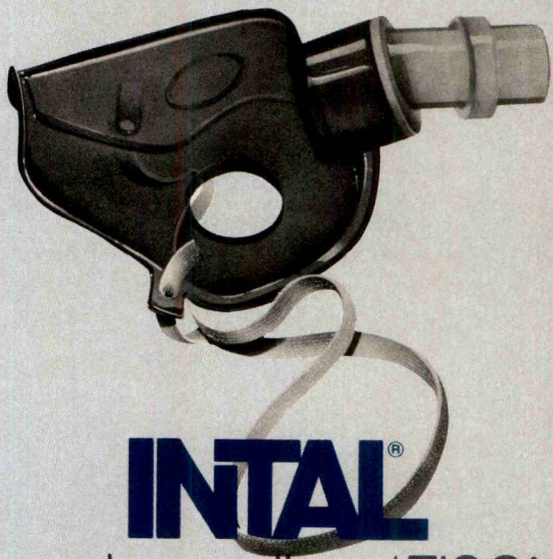
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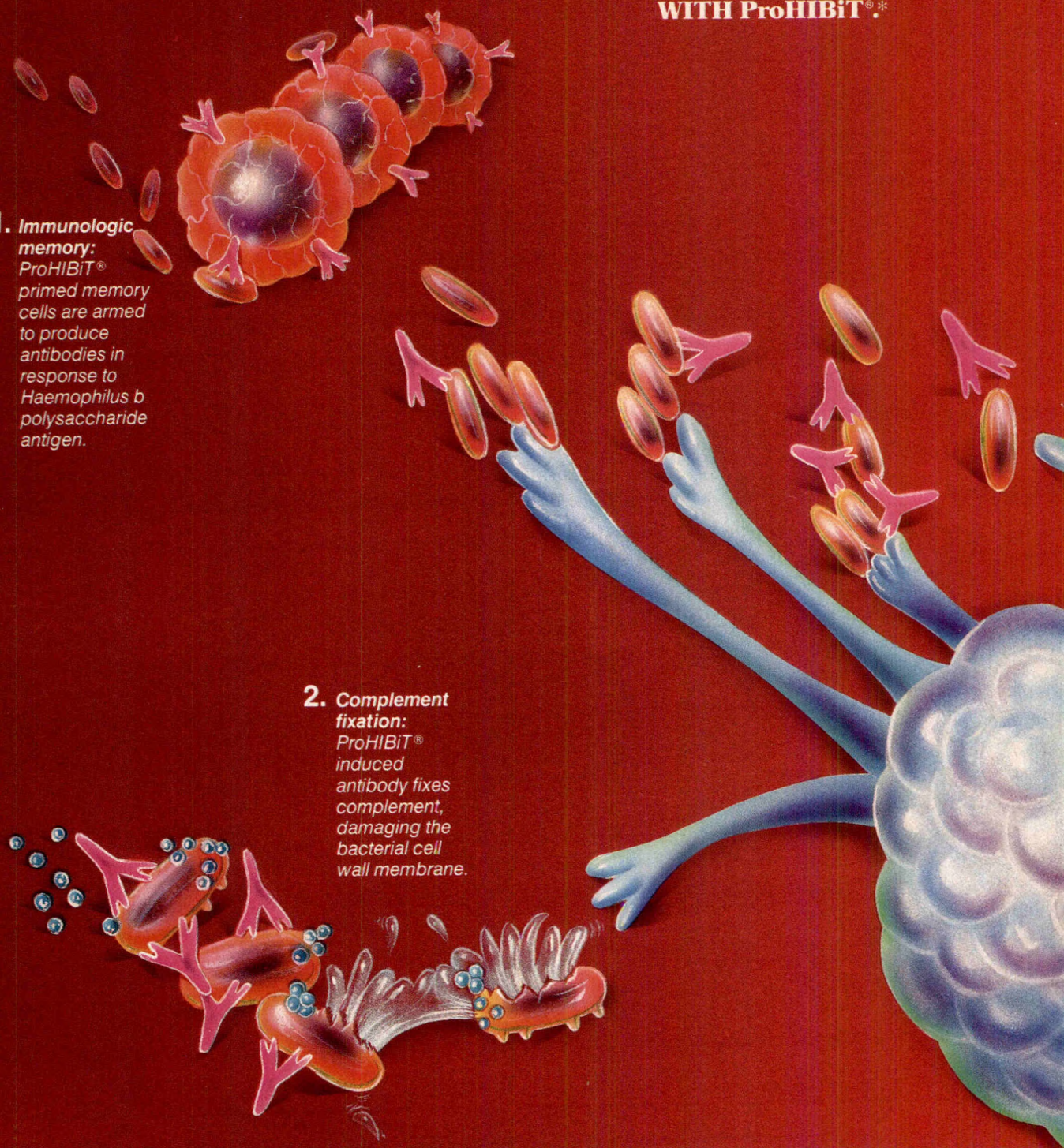
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BRIEF SUMMARY

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ProHIBiT is indicated for the routine immunization of children 18 months to 5 years of age against invasive diseases caused by *Haemophilus influenzae* type b. As with other vaccines, several days following administration of ProHIBiT are required for protective levels of antibody to be attained.

A booster dose of ProHIBiT is *not* required.

ProHIBiT will not protect against *Haemophilus influenzae* other than type b or other microorganisms that cause meningitis or septic disease.

No impairment of the immune response to the individual antigens was demonstrated when ProHIBiT and Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (DTP) were given at the same time at separate sites.

Because the safety and efficacy of ProHIBiT have not been established in children less than 18 months of age, ProHIBiT is not indicated for use in this age group at this time. Studies to establish the safety and efficacy of ProHIBiT in children less than 18 months of age are ongoing.

ProHIBiT IS NOT RECOMMENDED FOR USE IN CHILDREN YOUNGER THAN 18 MONTHS OF AGE.

CONTRAINDICATIONS

HYPERSENSITIVITY TO ANY COMPONENT OF THE VACCINE, INCLUDING THIMEROSAL AND DIPHTHERIA TOXOID, IS A CONTRAINDICATION TO USE OF THIS VACCINE.

WARNINGS

If ProHIBiT is used in persons with malignancies or those receiving immunosuppressive therapy or who are otherwise immunocompromised, the expected immune response may not be obtained.

As with any vaccine, ProHIBiT may not protect 100% of individuals receiving the vaccine.

PRECAUTIONS

GENERAL

As with the injection of any biological material, Epinephrine Injection (1:1000) should be available for immediate use should an anaphylactic or other allergic reaction occur.

Prior to an injection of any vaccine, all known precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible hypersensitivity to the vaccine or similar vaccines.

Any febrile illness or acute infection is reason to delay the use of ProHIBiT.

As reported with *Haemophilus b* polysaccharide vaccine, cases of *Haemophilus b* disease may occur in the week after vaccination, prior to the onset of the protective effects of the vaccine.

Special care should be taken to ensure that the injection does not enter a blood vessel.

A separate, sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another.

ALTHOUGH SOME IMMUNE RESPONSE TO THE DIPHTHERIA TOXOID COMPONENT MAY OCCUR, IMMUNIZATION WITH ProHIBiT DOES NOT SUBSTITUTE FOR ROUTINE DIPHTHERIA IMMUNIZATION.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

ProHIBiT has not been evaluated for its carcinogenic, mutagenic potential or impairment of fertility.

PREGNANCY

REPRODUCTIVE STUDIES — PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with ProHIBiT. It is also not known whether ProHIBiT can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ProHIBiT is NOT recommended for use in a pregnant woman.

ADVERSE REACTIONS

When ProHIBiT alone was given to over 1,000 adults and children, no serious adverse reactions were observed. Thrombocytopenia was seen in one adult but a causative relationship was not established.

When ProHIBiT was given with DTP and Inactivated Poliovirus Vaccine to 30,000 young infants, the rate and extent of serious adverse reactions were not different from those seen when DTP was administered alone. Allergic reactions such as urticaria were infrequently observed.

Selected adverse reactions following vaccination with ProHIBiT (without DTP) in subjects 16-24 months of age are summarized in Table.

TABLE
Percentage of Subjects 16-24 Months of Age Developing
Local Reactions or Fever to One Dose of
Haemophilus b Conjugate Vaccine (Diphtheria Toxoid-Conjugate)

	No. of Subjects*	Reaction %		
		6 Hours	24 Hours	48 Hours
Fever >38.3°C	281	1.1	2.1	1.8
Erythema	285	—	2.5	0.4
Induration	285	—	1.0	0.4
Tenderness	285	—	4.6	0.7

*Not all subjects had measurements at all time periods.

Other adverse reactions temporally associated with administration of ProHIBiT included diarrhea, vomiting, and crying and occurred at a frequency of ≤1.2%.

Adverse reactions in clinical evaluations among 689 children, 7-14 months of age, 24 hours after receiving a single dose of ProHIBiT, were observed and compared to 139 children who received a saline placebo. There were no significant differences in the reaction rates for fever, erythema, induration, and tenderness between the two groups.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for extraneous particulate matter and/or discoloration prior to administration whenever solution and container permit. If these conditions exist, vaccine should not be administered.

ProHIBiT is indicated for children 18 months to 5 years of age. The immunizing dose is a single injection of 0.5 ml given intramuscularly in the outer aspect area of the vastus lateralis (mid-thigh) or deltoid.

Each 0.5 ml dose contains 25 mcg of purified capsular polysaccharide and 18 mcg of conjugated diphtheria toxoid protein.

Before injection, the skin over the site to be injected should be cleansed with a suitable germicide. After insertion of the needle, aspirate to ensure that the needle has not entered a blood vessel.

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REFERENCES: 1. Data on file, Connaught Laboratories, Inc. 2. Weinberg GA, Granoff DM: Polysaccharide-protein conjugate vaccines for the prevention of *Haemophilus influenzae* type b disease. *J Pediatr* 1988;113:621-631.

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Resident Stress

Sir—Hoekelman¹ recently identified factors that lead to stress during residency training. He claimed that causes of stress go beyond long work hours and the severely ill population for whom residents care, and stated that the stress to which residents are exposed is accentuated by the uncertainty of their futures once training is completed.

Hoekelman suggested many changes that residency programs can adopt to reduce the stressors that are inherent in the present system. However, significant changes in residency training will not be implemented until members of the medical faculty begin to understand the transformations that have begun to take place in the provision of health care. These have occurred as a result of the corporate restructuring of health care systems. Since the rise of what Relman² terms the *medical-industrial complex*, hospitals are often managed by business executives rather than the traditional physician administrator who once managed residency training and hospital services. In light of the changes in the management of hospital systems, faculty need to be advocates for the physical and educational needs of the house staff. This would enable residency training programs to meet the changing needs of the health care organization.

In today's medical marketplace, the expertise offered by the business community is necessary to maintain the viability of health care facilities. However, profitability factors may not translate into the most educationally sound residency experience where a balance exists between service and education. Tension between a resident's service commitment and educational pursuits may be intensified by decisions made by corporate man-

agers who are insensitive to or unaware of the demands of the residency process.

In light of these concerns, Hoekelman's suggestions for changes in the environment in which residents learn is timely and appropriate. Hoekelman's perspective finds a blueprint for an approach to the improvement of physician education described by Jonas.³ In his book, Jonas examines the US health care provision system and the process through which graduate physicians progress to emerge as "doctors." He contends that the present system, on which medical training and practice is based, fosters in itself an unhealthy approach to both work and education. Our disease-oriented health care system gives minimal support to prevention and health maintenance endeavors on the part of physicians-in-training.

In the 1980s, medical centers have emerged as sites for disease treatment and acute care intervention. Public policies and financial resources for health care are developed to cope with disease rather than to encourage health promotion and disease prevention. A nonprevention orientation is entrenched even within the physician training process, which ignores the requisites of health and stands as the model for an unhealthy living and learning environment.

Jonas³ addresses Hoekelman's concerns and proposes a preventive, health-promotion-based model for medical education entitled Health Oriented Professional Education (HOPE). HOPE includes five points that should be incorporated into the philosophy and curriculum of medical schools and residency programs. The proposal encourages (1) a prevention-based orientation for a program that emphasizes outpatient care focused on health maintenance and preventive

screening; (2) faculty attitudes that foster student/resident health, including reasonable expectations for resident responsibilities and encouraging postcall residents to complete their work early and go home to sleep; (3) expressed emphasis on active learning, utilizing a problem-based mode of teaching to provide feedback and build self-esteem; (4) increased use of ancillary services and the incorporation of computer technology to simplify menial tasks and enable the resident to reduce his or her secretarial responsibilities; and (5) encouraging physician-teachers to seek formal training in the educational process to enhance the quality of medical education.

The Jonas³ model provides one approach to the reduction of resident stress. Other approaches exist as well. The common theme among various approaches is that residency training must incorporate principles of healthy living while meeting the service requirements and educational objectives of the programs.

As Hoekelman stated, pediatric and other medical educators are largely responsible for the ill effects of the residency training programs on practitioners. The improvement of residency training depends on the commitment of the faculty to engage corporate administration in the needs of the residents and to serve as sentinels for the residents during this process. Residency training should occur in an environment that provides patient care while ensuring healthy personal and professional development among the participants.

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Stress During Residency Training

Sir:—We read with interest the article by Hoekelman regarding stress experienced during pediatric residency training in the February 1989 issue of *AJDC*.¹ This article adequately outlined the problem of resident stress and proposed some very useful solutions.

I think we can all recall similar discussions and proposed solutions dating back at least 15 years. Very little has changed, presumably because it has not served the interest of hospitals to follow through on these and other means of resolving the issue of stress during residency training. In New York State in particular, we have been presented with recommendations by the State Department of Health regarding limitations on working hours, the use of nonphysician personnel for responsibilities such as blood drawing and starting of intravenous lines, and the use of computers to facilitate retrieval of laboratory results. Very few programs are even attempting to comply with these regulations by the July 1989 deadline, again illustrating the difference between what hospitals say they want for residents and what they are willing to provide.

With regard to Hoekelman's proposals, I wonder how effective restricting the maximum shift to 29 hours would be in reducing fatigue and stress, particularly if this schedule is followed on an every third night basis. We feel that if one truly wishes to reduce resident fatigue it is insufficient to reduce the maximum shift simply from 34 to 29 hours. Doing away with moonlighting is a method of uncovering another potential source of resident stress, that is, financial stress. Many of our first-year residents have debts related to undergraduate and medical education that are in excess of \$30 000. These residents also have families. To expect them to repay these debts and manage a family on the usual house staff salary puts additional pressure on a house officer. The issues of ancillary personnel and computerization are not addressed by Hoekelman, yet there is certainly no greater waste of a resident's time than to wait on the telephone until a technician can re-

cover a laboratory result or to spend hours performing technical procedures long after he or she has been credentialed in these same procedures.

In our pediatric residency program, we have adopted a maximum 16-hour shift in inpatient ward areas and will have maximum 24-hour shifts on an every fourth night basis in intensive care areas by July 1989. Postgraduate level 1 residents have at least one 24-hour period of relief from direct patient care activities each week. Work schedules average 80 hours or less for each 4-week module. Moonlighting is allowed as long as the maximum shift does not exceed 24 hours and the maximum hours worked per week does not exceed the 80-hour limit. We have moved ahead with educating nurses and other nonmedical personnel in the starting of intravenous lines and drawing of blood. While there are imperfections in the system (which we hope to resolve), it is clear that the level of fatigue and emotional stress among our current postgraduate level 1 residents is substantially less than in past years. We hope to have available a more formal evaluation of our experiences with these modifications in the near future. The purpose of this commentary is to reassure those institutions that wish to move forward with similar revisions that house officers can benefit from such changes if the programs are willing to make them.

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Strategies to Prevent Household Electrical Injuries in Children

Sir:—The article by Baker and Chiaviello¹ in the January issue of *AJDC* is an important addition to the scanty literature on children's electrical injuries and strategies to prevent them. The American Academy of Pediatrics' *Guidelines for Health Supervision*² and five of seven widely used pediatric textbooks that we reviewed suggested the use of outlet plugs as a strategy to prevent these injuries.³⁻⁹ None of these references detailed the various types of outlet plugs available

or their potential limitations and dangers. Baker and Chiaviello described some of their limitations, but we believe that there are other important considerations and potential problems with them that deserve description.

As Baker and Chiaviello noted, "infant toys should not simulate common household items. . . ." Similarly, we believe that safety items should not simulate toys, especially if they themselves are potentially harmful to children. This, unfortunately, is the case with many outlet plugs. Some are actually embossed with attractive designs, such as bears (a common transitional object for children), thereby enticing children to remove them from outlets. Many of these devices are also small enough to pose the danger of aspiration to children.

The Consumer Product Safety Commission and American Academy of Pediatrics collaboratively created the commercially available No Choke Testing Tube (Fig 1). This practical device serves as the gauge for the current federal small parts and toy safety regulations regarding the minimum size allowed for any object intended for use by children under the age of 3 years. Nine of 10 outlet plugs purchased at Boston, Mass, supermarkets, hardware stores, and toy stores were small enough to fit into the No Choking Test Tube, and thus failed the test. In addition, any safety device that requires behavior change has reduced protective value when compared with devices that automatically offer protection. Most outlet plugs currently available must be removed whenever the outlet is used and then put back into the outlet. It is likely then that they will be used only sporadically. This may increase the risk to toddlers if parents, unaware of their potential danger, leave the plugs lying about.

As part of Boston's Childhood Injury Prevention Program, pediatricians at selected health centers and hospital-based clinics, day-care providers, and public health nurses have distributed outlet plugs to families for the past 3 years. A number of health care providers and parents have observed children playing with the small outlet plugs and putting them into their mouths. Furthermore, people making home visits have noted not only unprotected outlets but loose outlet plugs in families' homes.

Baker and Chiaviello's proposed outlet cover is in principle laudable. It addresses one limitation of outlet plugs; that is, the proposed outlet

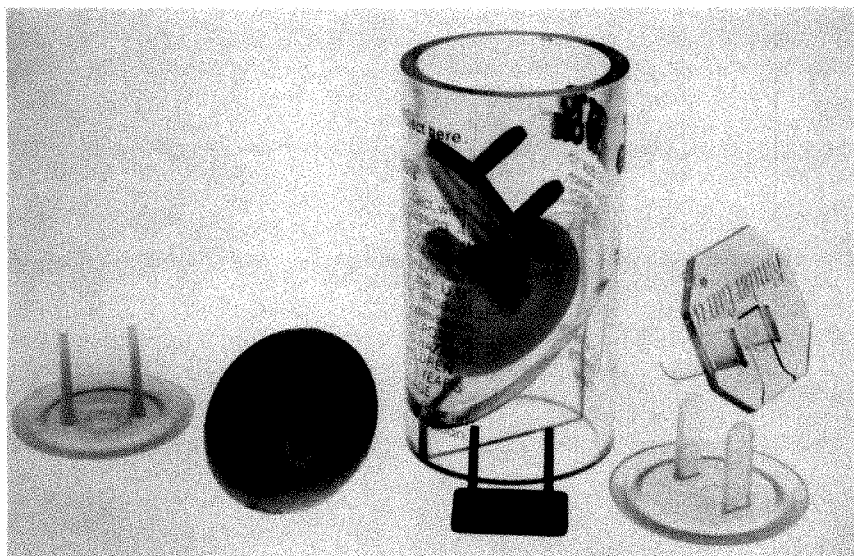


Fig 1.—No Choke Testing Tube and an assortment of outlet plugs.

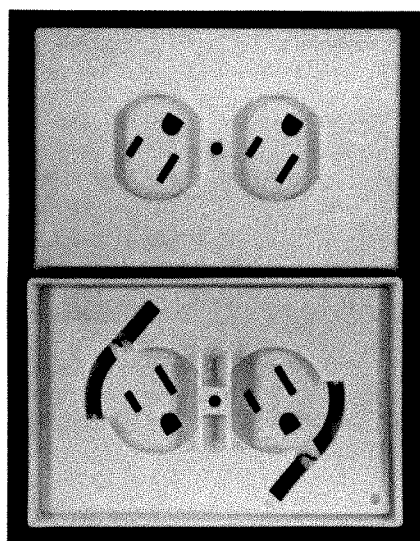


Fig 2.—Sanitoy outlet cover, front and rear views.

cover is permanent once installed. Any safety device that requires a three-step procedure, such as the one they propose, however, seems unlikely to be used regularly and appropriately by large numbers of individuals. We distribute an outlet cover manufactured by Sanitoy (Fitchburg, Mass) (Fig 2) that requires a one-step procedure with either a two- or three-pronged electrical plug. This cover requires only one screw and is a permanent fixture. It is extremely difficult to gain access to the outlet holes by using anything but an electrical appliance plug. The automatic release and closure prevent access to the outlet once an appliance is unplugged. In the case of double outlets, each one is

independently closed or opened depending on use. This cover is fitted over the existing outlet plate and no contact with exposed wires is necessary or possible, whereas the cover proposed by Baker and Chiaviello would require replacing the regular outlet plate.

Injury-prevention activities must be easily integrated into everyday habits and routines if they are to be widely adopted by families. We must also be cautious that we do not distribute or encourage the use of injury-prevention technology without educating parents about the technology's limitations and potential dangers.

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The authors have no commercial or proprietary interest in the Sanitoy outlet cover, nor do they have any financial interest (as consultant, reviewer, or evaluator) in the Sanitoy outlet cover.

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'Mangoism'

Sir.—We recently cared for a 16½-month-old Equadorian boy who presented with orange coloration and failure to thrive.

The child presented to the clinic for routine health care. Concern was raised about the child's growth. He weighed 8.3 kg (less than the fifth percentile), showing a 28-g gain in 11 weeks. His height was 76 cm (10th percentile) and his head circumference was 46.5 cm (10th percentile). The family indicated that this child had become difficult to feed and denied any specific food preferences.

The physical examination was remarkable for a very slight toddler whose skin was an intense orange color that was most obvious on his palms and soles. There was no scleral icterus. The remainder of the examination was unremarkable. Because of concern about this child's poor weight gain and unusual coloration, he was admitted to the hospital.

At the time of admission, the patient's hemoglobin level was 127 g/L, his hematocrit value was 0.39, and his white blood cell count was $9.8 \times 10^9/L$, with a differential cell count of 0.35 polymorphonuclear cells, 0.63 lymphocytes, and 0.02 monocytes. The urinalysis showed a pH value of 5; the results of the glucose, ketones, and protein tests were negative. The urine culture yielded no growth. The serum glucose level was 4.8 mmol/L. The total bilirubin value was 5.13 $\mu\text{mol/L}$, thyroxine level was 102 nmol/L, triiodothyronine uptake was 0.38, and thyroid-stimulating hormone was 4.0 mU/L. Electrolyte levels and chemistry profiles were within normal limits.

A diet history eventually obtained from the mother and family indicated that this child was fed approximately 16 ounces daily of whole milk, cereals,

commercially prepared pureed or strained meats, soups, and sweet fruits, especially mangoes. The mangoes were the only food he regularly ate well, generally consuming about 8 oz daily in the form of commercial baby food over the previous 2 months.

In the hospital, the boy was found to be a difficult eater with significant acting-out patterns at meal times. Over time, the child learned to self-feed with his fingers and to accept a more balanced assortment of food-stuffs. With the omission of mangoes from his diet, the orange color faded within 2 weeks. The child began to gain weight. The family did not accept a behaviorally based cause of his failure to thrive and signed the toddler out of the hospital against medical advice.

We conclude that the skin coloration was due to carotenemia and that both the carotenemia and the failure to thrive occurred as a result of overeating a low-calorie, carotene-rich fruit, the mango.

Carotenemia can be associated with a multitude of clinical disorders or with overzealous consumption of carotene-rich plant foods.¹ Reported cases of dietary carotenemia have mainly discussed the overconsumption of vegetables, such as pumpkin² and notably carrots.^{1,3-6} Although carotenemia is assumed to occur from the excessive consumption of carotene-rich fruits, it is rarely reported. Sharman⁴ described a Japanese woman who developed a yellow coloration from eating oranges.

Carotenemia itself is benign and the usual treatment for the symptoms is withdrawal of the carotene sources. However, we would like to stress the importance of this condition as a marker for possible abnormal dietary practices. This case stressed several points for us.

1. An immoderate intake of one food usually implies a disproportionate intake of others, especially in children.
2. The traditional association of carotenemia with carrots should be broadened to include all deeply colored fruits. Consumption of exotic fruits, such as papaya and mangoes, is increasing with the availability of intercontinental transport and the demand for them by immigrants from southern climates.
3. The physical form of the carotene may be more important than the amount in children because absorption of carotenoids apparently increases

the more a food is pulverized.⁷ Strained mangoes are potentially more carotenemic than perhaps whole fresh mangoes in an equal amount.

4. Along with possible protein-calorie malnutrition, carotenemia may be seen as another consequence of prolonged overuse of strained foods.

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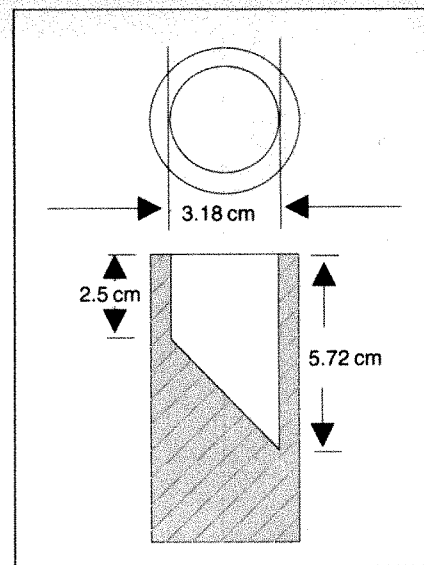
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Choking on a 'Large' Object: Applications for Regulation and Practice

Sir.—Choking on foreign bodies is a preventable cause of morbidity and mortality in small children. In 1985, small toys or their parts were responsible for 12 000 such injuries in the United States, with 18 fatalities reported during the period from January 1985 to September 1986.¹ We describe a child who suffered near-fatal choking on an object considered "large" by current standards.

Patient Report.—A 10-month-old male infant and his 3-year-old sister were seen for well-child visits by their pediatrician, who administered the Denver Developmental Screening Test. That evening, their father found the infant thrashing about on the bed where he and his sister had been playing, his head extended and eyes rolled back. He felt a hard object in the child's mouth but was unable to remove it. The child became dusky and limp. After 2 to 3 minutes, a 2.5-cm wooden cube was dislodged. The child's mouth was bloody and he was thought to be in cardiorespiratory arrest. Cardiopulmonary resuscitation was initiated and continued for an estimated 3 minutes before the child became responsive. Twelve minutes after receiving the call, paramedics found the child to be alert and in no distress. In the emergency department, examination by an otolaryngologist revealed a 5-mm superficial tear in the right anterior tonsillar pillar without active bleeding; the child was otherwise well. The sister later stated that she had kept the



Small parts test fixture.³

block, which had come from the Denver Developmental Screening Test kit, and had later put it into her infant brother's mouth. Follow-up examination 2 weeks later showed complete healing of the pharyngeal lesion.

Comment.—The size of small toys and their parts marketed in the United States is regulated by the Federal Hazardous Substances Act. The Consumer Product Safety Commission (CPSC) has established a method for determining whether an article presents a choking hazard: the sale of toys and other articles intended for use by children under age 3 years is prohibited if they are small enough to fit entirely within a truncated cylinder with a diameter of 3.18 cm and depth ranging from 2.5 to 5.72 cm (Figure). Based on the recommendations of the American Academy of Pediatrics,² this size was thought to represent the size above which complete airway obstruction is unlikely to occur.

However, the CPSC has reported 194 choking incidents in children, including 37 deaths, caused by objects larger than the cavity in the small parts test fixture for the period from July 1973 to May 1983.³ Affected children ranged in age from 1 month to 4 years; one half were 4 to 8 months old. For the 136 objects whose size was available, 78 (57%) had diameters larger than 3.28 cm, and were implicated in 5 of the fatalities. Only 4 objects (4%) larger than 4.29 cm in diameter were involved in choking episodes, none of them fatal. At least 41 incidents (36%), including 10 fatalities were caused by objects with a diameter smaller than that of the test fixture but with length longer than the 5.72-cm depth of the test fixture. The CPSC

report concluded that "objects with diameters of 1.65 inches [4.19 cm] or less are choking children . . . it appears that the 1.25 inch [3.18-cm] dimension of the small parts tester is not adequate to prevent penetration of an object into the mouth."

The regulation has not been changed, however, and in April 1987 the Consumer Federation of America (CFA) and the New York State Attorney General petitioned the CPSC to increase the diameter of the small parts test standard.^{4,5} Based on the CPSC data, the petitioners contended that the minimum diameter permitted for toys for small children should be increased to 4.3 cm, and that the length requirement was irrelevant to preventing choking. This diameter equals the size of the infant mouth and represents the minimum size required by the current pacifier regulation.³ Such a standard would have prevented all but 5 of the 136 incidents reported by the CPSC, and all of the fatalities.

In the patient we describe, near-fatal choking was caused by a wooden block from a Denver Developmental Screening Tests kit, which measures 2.5 cm on each side and has a diameter of 3.6 cm. This is larger than the 3.18 cm diameter of the current test fixture, but smaller than the 4.3-cm diameter proposed by the Consumer Federation of America/New York State petition. Pediatricians should be aware that objects considered safe by current standards can cause potentially fatal choking in small children, including Denver Developmental Screening Test blocks from the clinic or office that find their way into homes with their young patients.

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Mucocutaneous Lymph Node Syndrome: Is There a Relationship to Mercury Exposure?

Sir:—We were interested in the article by Krowchuk et al¹ in the November 1988 issue of *AJDC* about the occurrence of exanthem limited to the diaper area in a 21-month-old male child diagnosed as having Kawasaki disease. We were disappointed that the authors failed to note the type of diapers used by this child. This case brings to mind a 1981 report² of acrodynia, or "pink disease," in thousands of infants in Buenos Aires, Argentina, who were poisoned by mercury from commercially laundered diapers. The causative compound was phenylmercury, which was added to the laundering process because it is such an effective fungicide and reduces the odors produced during washing and storing. A causal relationship of Kawasaki disease and inorganic mercury poisoning was first suggested by Cheek,³ following observations that acrodynia has many symptoms similar to mucocutaneous lymph node syndrome (MLNS).

Acrodynia, or "pink disease," was traced by Warkany and Hubbard⁴ to "medicinal" use of teething powders containing calomel (mercurous chloride) and mercury-containing ointments for the treatment of impetigo. Mercurials were also widely used as antihelminthic agents. Acrodynia is characterized by hyperemic pharynx and lips, a markedly red strawberry tongue, and loss of teeth. In the peripheral extremities, symptoms include indurative edema, emaciation and erythema of the skin, and membranous desquamation with pink to red fingertips, palms, and soles. Other salient signs and symptoms include bilateral conjunctival hyperemia, polymorphous exanthem, cervical adenopathy, photophobia, arthralgia, thromboses, anorexia, and irritability. Fever and coronary artery aneurysms have not been associated with acrodynia. Naturally, not every instance shows the same profile of effects, and some symptoms, particularly during the early stages of the disease, are so nonspecific that the pediatrician may be easily misled. While the similarity

in symptoms between MLNS and acrodynia does not necessarily prove the identity of the two diseases, the clinical manifestations of MLNS, justifiably, led investigators to question the role of inorganic mercury in its origin. Although Kawasaki⁵ failed to detect elevated mercury levels in his patients' hair, reports^{6,7} of elevated urinary mercury excretion in patients with MLNS led some investigators⁶ to suggest that elevated IgE levels reflect an allergic aspect and a hypersensitivity reaction to inorganic mercury poisoning.

Mercury, a ubiquitous metal, exists in a number of physical and chemical forms. Inorganic mercury exists in the metallic form (Hg^0), in the mercurous form (Hg_2^{2+}), and in the mercuric form (Hg^{2+}). Both the mercurous and mercuric cations can form a number of inorganic compounds. In addition, the mercuric cation is able to form covalent bonds with carbon atoms to produce organic species of mercury. Biomethylation reactions in fresh and saline water carried out by methanogenic bacteria result in the formation of organic mercury, which accumulates in the aquatic biota and thereby enters the human food chain. Today, human exposure is mainly to two forms of mercury species: occupational exposure to the vapor of metallic mercury, and exposure to methylmercury (MeHg) via the food chain, primarily from fish and its products.

Having a flameless, cold-vapor atomic-absorption technique at our disposal, we further explored a possible relationship between inorganic mercury exposure and MLNS. The urine is the best indicator of long-term exposure to inhaled mercury vapor, and hair is a valuable indicator in the assessment of MeHg's body burden. When the distribution process of MeHg is completed, the concentration ratio between hair and blood remains constant and the hair concentration of the organometal is a fixed multiple of its blood concentration ($\times 250$). Thus, if measured longitudinally, hair samples can catalog a month-to-month variation in blood MeHg concentrations and a history of exposure. Other forms of mercury, because of their conversion to divalent mercury, behave in a similar fashion to inhaled mercury vapor.

Three pediatric patients admitted to Strong Memorial Hospital between October 1985 and May 1986 with a diagnosis of MLNS were examined for evidence of elevated mercury levels. The results obtained are as follows:

Patient No.	Urine, ng/mL		Hair, μ g/g
1	0.95		0.52
2	0.47		1.19
3	2.32	Not detectable	

("Normal" values for mercury in urine and hair are less than 20 ng/mL and <7.5 μ g/g, respectively. The technique has a sensitivity of approximately 0.5 ng of mercury in biological samples.)

At present the cause of Kawasaki disease remains unknown. In a small cohort of patients with MLNS, we failed to corroborate a link between MLNS and inorganic mercury exposure. No potential source of mercury exposure could be identified in these three patients, and mercury levels were not elevated. It remains conjectural whether MLNS is a common pathway for multiple pathogenic factors, possibly including inorganic mercury poisoning. While our results refute the hypothesis that, by itself exposure to inorganic mercury alone is responsible for MLNS, we must systematically continue the search for potential causative factors.

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In Reply.—We appreciate the thoughtful comments of Drs Aschner and Aschner regarding the possible relationship of mercury exposure and the development of Kawasaki disease. As they note, a number of less obvious or frankly occult exposures to mercury exist, including that resulting from the use of certain diaper rinses. The patient described by us,¹ however, wore

of the Ultrapampers variety. To our knowledge, mercury is not used in the manufacture of these products, thus obviating diapers as a source of potential exposure.

Acro-dynia is appropriately included in the differential diagnosis of the cutaneous and systemic manifestations of Kawasaki disease. While Kawasaki disease and acro-dynia share certain similarities of presentation, these processes may be distinguished by their unique clinical manifestations.^{2,3} Kawasaki disease has a sudden onset and a self-limited course, with the majority of overt clinical findings resolving within 1 month. In contrast, acro-dynia manifests an insidious onset and protracted course. Fever of 5 or more days' duration, uncommon in patients with acro-dynia, is a hallmark of Kawasaki disease. Although bilateral conjunctival hyperemia may occur in both disorders, photophobia is more commonly observed in acro-dynia, affecting more than one half of all patients. Both Kawasaki disease and acro-dynia produce changes involving the extremities, including erythema, swelling, and peeling. However, while arthralgias or arthritis may occur in Kawasaki disease, a prominent manifestation of acro-dynia is severe pain of the feet and hands that may limit ambulation or cause patients to rub their hands together. The erythema associated with acro-dynia has a distinctive pink or scarlet hue (hence, the name "pink disease") that, early in the course of the disease, involves the distal portions of the nose, fingers, and toes.³ Other clinical findings unique to acro-dynia include weakness, hypotonia, insomnia, ulcerative gingivitis, and loss of teeth.^{2,3} Kawasaki disease and acro-dynia are each associated with the appearance of an exanthem. As noted recently, the exanthem of Kawasaki disease is frequently concentrated in, or may be limited to, the perineum.^{1,4,5} While coronary artery aneurysms are not known to occur in acro-dynia, they are a well-recognized complication of Kawasaki disease that was observed in our patient.

Even though acro-dynia and Kawasaki disease share certain similarities, each exhibits a unique natural history and distinctive clinical manifestations. Although current epidemiologic and laboratory information suggests that Kawasaki disease may have an infectious origin,⁶ Drs Aschner and Aschner offer sound advice when they suggest that the search for other potential causative factors should continue. Until a causative agent is identified, the

might be the result some environmental insult cannot be excluded.

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Age, Gender, and Metabolic Control in Children and Adolescents With Diabetes

Sir.—Adolescent girls with insulin-dependent diabetes mellitus (IDDM) have been found to have worse metabolic control than younger girls¹ and older women² with IDDM. However, the evidence is inconsistent regarding whether adolescent girls have worse control than adolescent boys.^{1,3} The sources of the purported poor metabolic control in adolescent girls are not clear, although several explanations have been proposed. It is widely believed that interactions of physiological concerns, social pressures, and physiological changes associated with adolescence contribute to the difficulties experienced by these individuals. Educational approaches to improving metabolic control are based in part on the hypothesized relationship between knowledge about diabetes and metabolic control. However, the evidence indicates that knowledge is unrelated, or even inversely related, to metabolic control.^{1,4}

Our study addressed these questions: (1) Do older girls demonstrate poorer metabolic control than boys and younger girls? (2) If older girls do have difficulty maintaining adequate control, is this due to inadequate knowledge about diabetes?

Patients and Methods.—The 23 girls and 17 boys with IDDM in this study ranged from 8 to 19 years of age (mean \pm SD, 13.7 \pm 2.2

years of age) and were recruited from a group of patients who received medical care at a juvenile diabetes clinic at the Duke University Medical Center, Durham, NC. Of the 40 subjects, 39 were white and 1 was black. Participation in this research was voluntary and was decided on the basis of parental and child consent. Subjects completed questionnaires in examination rooms during the course of their visits.

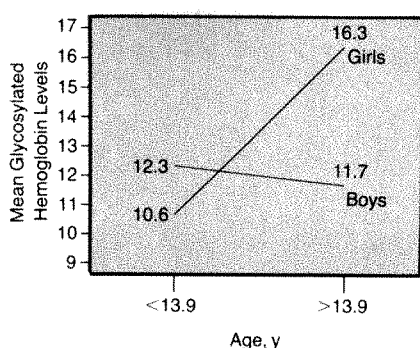
Diabetic control was assessed through the measurement of glycosylated hemoglobin levels (GlyHb) by affinity chromatography. This procedure was part of the regular clinic visit protocol. The GlyHb values typically ranged from 4.2% to 8.0% in individuals without diabetes. In our study, the GlyHb levels ranged from 6.8% (indicating good control) to 22.9% (indicating very poor control), with a mean value of 12.58% (4.15, SD).

A version of the test of diabetes knowledge by Johnson et al⁵ was used to assess knowledge of diabetes care. From the original set of 36 questions, 26 were chosen by a pediatric endocrinologist at the Duke University Medical Center Clinic as consistent with the treatment philosophy approach employed at the clinic. Johnson et al reported the split-half reliability of their measure to be .84, which is quite adequate. In our study, the scores ranged from 15 to 25 on this measure (mean, 20.55; SD, 2.17).

A two \times two analysis of covariance (ANCOVA) was used to evaluate the impact of sex (male, female) and age group (<13.9 years of age, \geq 13.9 years of age) on the dependent variable, GlyHb. The age group division was determined on the basis of a median split. Diabetes knowledge was evaluated and controlled for by including it as the covariate in the analysis.

Results.—The 4-year age-gender subgroups were composed of 13 younger girls (mean age, 12.3 years), 7 younger boys (mean age, 11.0 years), 10 older girls (mean age, 15.9 years), and 10 older boys (mean age, 15.2 years). The mean GlyHb values for younger boys and older boys with IDDM were 12.3% and 11.7%, respectively. For younger girls and older girls with IDDM the mean values were 10.6% and 16.3%, respectively. The ANCOVA indicated no significant contribution by either the covariate (ie, diabetes knowledge) or the main effect for sex. While the main effect for age group was significant ($F [1,35] = 4.21, P < .05$), this effect was explained entirely by the significant interaction of sex by the age group ($F [1,35] = 6.25, P < .02$). To evaluate the meaning of this interaction, simple main effects were calculated, indicating that older girls had worse metabolic control than younger girls ($F [1,35] = 14.01, P < .01$) and had control than older boys ($F [1,35] = 8.48, P < .01$) (Figure).

Comment.—The finding that metabolic control was worse in older girls is consistent with results from most prior



Age \times sex group interaction for metabolic control.

research.^{1,2} Furthermore, this pattern apparently cannot be explained by a lack of knowledge about diabetes care. Several other investigators also have reported knowledge to be unrelated, or even inversely related, to diabetic control.^{1,4} Factors other than self-care knowledge, then, must be contributing to the older girls' difficulties with diabetes. It has been suggested that the social demands and/or hormonal changes that accompany puberty in girls may lead to diabetes management problems. If the poor control is largely due to hormonal factors, changes in the degree of adherence to a health care regimen may have only minimal impact on the disease.

Noncompliance among these individuals, then, may arise partly out of the feeling that compliance is a futile endeavor, since their diabetes is experienced as an unmanageable disease. Additionally, although the gender differences reported here are not explained by this research, it is of note that decreased sensitivity to insulin has been found in pubertal children with and without diabetes.^{6,7} Clearly, it is important to focus future research efforts on adolescent girls with diabetes to try to determine the source of their difficulties with their illness and, if possible, to help them achieve better metabolic control.

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Hyperglycemic Acidosis With Mortality in Kearns-Sayre Syndrome

Sir.—Kearns-Sayre syndrome (KSS) is a rare multisystemic disorder, usually described as the clinical triad of chronic progressive ophthalmoplegia, retinitis pigmentosa, and cardiomyopathy.¹⁻³ There is a pathologic degeneration of the central nervous system (ie, spongiform degeneration of the brain) and skeletal and pancreatic abnormalities.^{4,5} Sudden death in patients with KSS has been primarily attributed to the cardiac conduction defects and cardiomyopathy.³

Recently, the association of chemical diabetes and hyperglycemic acidotic coma has been documented in the ophthalmology literature.⁶ We describe three patients with KSS who we believed died secondary to complications related to KSS and hyperglycemic coma. We would like to bring this potentially devastating problem to the attention of the pediatrician.

Patient Reports.—PATIENT 1.—A 14-year-old boy was first seen at 10 years of age with bilateral ptosis, proximal skeletal myopathy, and external ophthalmoplegia. At that time, the results of his cardiac examination were normal, but his electrocardiogram demonstrated left-axis deviation and a right bundle branch block pattern. Three years later, the patient developed a 2:1 and 3:1 block associated with syncope. A permanent demand ventricular pacemaker was inserted, and clinical improvement resulted. During that hospitalization, the diagnosis of KSS was made.

Five months later, prednisone therapy was initiated, 100 mg every other day orally, for progressive muscle weakness. Fifteen days later, the patient suddenly collapsed and was unresponsive on arrival

at the University of Miami/Jackson Memorial Hospital emergency department. His mother gave the medical history of polyuria and polydipsia 2 days prior to admission. The electrocardiogram showed normal ventricular pacing. The serum glucose level was greater than 27.8 mmol/L. The blood gas analysis revealed a pH level of 6.88 and a base deficit of -25. Shortly thereafter, the patient had a cardiopulmonary arrest and could not be resuscitated.

PATIENT 2.—An 8½-year-old boy presented with the clinical triad of KSS, complete atrioventricular block, and syncope. A permanent epicardial pacemaker was surgically implanted. At that time a muscle biopsy revealed the characteristic "ragged red fiber myopathy," and the diagnosis of KSS was confirmed.

Over the next 4 years, the patient experienced further growth retardation, progressive ataxia, and proximal muscle weakness. When the patient was 12 years of age, a neurologist initiated prednisone treatment, 25 mg/d, for progressive muscle weakness. Within the next 4 days, polydipsia, polyuria, and polyphagia ensued. A cardiopulmonary arrest occurred, and the patient was taken to the University of Miami/Jackson Memorial Hospital emergency department. An electrocardiogram demonstrated normal ventricular pacing. The arterial blood gas analysis demonstrated a pH level of 6.97 with a base deficit of -25; the serum glucose level was 53.7 mmol/L. Medical treatment failed to correct the metabolic derangement and maintain adequate cardiac output. The patient died within 24 hours of admission.

PATIENT 3.—A 9-year-old boy with KSS required a ventricular-demand pacemaker because of presyncope attributed to complete heart block. Progressive skeletal myopathy caused the patient to be debilitated, and steroid therapy was initiated. He collapsed in school and was taken to a local hospital emergency department. Initially, the diagnosis of pacemaker failure was entertained. However, a random serum glucose level was 57.7 mmol/L; glucose was present in his urine but ketonemia was not evident. The arterial blood gas analysis demonstrated a severe metabolic acidosis. Normal pacemaker function was present on the electrocardiogram. Despite aggressive therapy, the patient died within 6 hours.

Comment.—Over the past 12 years, there have been at least nine reported cases of KSS with associated chemical diabetes, defined by an abnormal glucose tolerance level and/or an elevated fasting blood glucose level.^{4,6,7} To date, there has been no satisfactory explanation for the appearance of this hyperglycemia.

Postmortem examinations of the three patients described herein revealed myocardial histologic changes characteristic of KSS: irregular muscle fibers with large nuclei and fatty and fibrotic infiltration of the conduc-

tion system. Of interest was the pathologic description of the pancreas in two patients; there was a decrease in the number of pancreatic islet cells, along with abnormal edematous mitochondria, fatty infiltration, and fibrosis. The third case demonstrated abnormally large islet cells.

It is known that KSS is associated with pathological degeneration of the myocardial conduction system, the central nervous system, the musculoskeletal system, and, as evidenced in these cases, in the pancreatic cells. The abnormality in the pancreas could result in a predisposition to hyperglycemia.

It is well appreciated that steroid-induced hyperglycemia is caused by an increase in gluconeogenesis and a decreased glucose utilization,⁸ which can result in significantly elevated blood glucose levels. This differs from insulin-dependent or type I diabetes, which is defined as a total deficient endogenous insulin state.⁹ This occurs when a sufficient number of beta cells are destroyed by various causes (ie, autoimmune, viral, or toxic destruction) to result in a decrease in insulin secretion so that hyperglycemia occurs.¹⁰

In the presence of pathologic degeneration of pancreatic islet cells as exhibited in these reported cases, it is reasonable to assume that the steroids resulted in the hyperglycemia and metabolic abnormalities. Their deleterious effects superimposed on the central nervous system and cardiac pathologic findings could have resulted in their death.

Physicians caring for patients with KSS should routinely measure fasting serum glucose levels and perform a glucose tolerance test.^{4,6,7} Special attention should focus on any symptoms suggestive of hyperglycemia, such that aggressive management can proceed if indicated. We recommend that steroids not be used in the management of the associated skeletal myopathy seen in KSS due to its diabetogenic effects.

Finally, if a patient with KSS has a sudden catastrophic event, immediate attention should focus on pancreatic glucose function and the resulting metabolic derangement as well as cardiac and cerebral abnormalities.

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Complex Congenital Heart Disease After In Vitro Fertilization

Sir.—Congenital heart disease is a rare complication in newborns conceived by in vitro fertilization and embryo transfer.¹⁻³ We describe a patient with a complex congenital heart disease born after this procedure. The mother was 28 years old and had had previous abortions that caused infertility. The blastocystic implantation was accomplished in Rome, at another institution. The newborn, a chromosomically normal female, was born at the 34th week of gestation following an uncomplicated pregnancy. Delivery was normal, and birth weight was 2300 g. Cyanosis was noted at birth, and cardiac catheterization revealed pulmonary atresia with a large ventricular septal defect. The pulmonary arteries were supplied by a ductus arteriosus, the aorta arose completely from the right ventricle surrounded by a muscular infundibulum, and a persistent left superior vena cava drained into the left atrium through an unroofed coronary sinus. The patient underwent a right Blalock-Taussig shunt as a neonate, and the definitive correction was successfully performed when she was 20 months of age, with a Rastelli procedure involving closure of the ventricular septal defect and placement of a valved conduit between the right ventricle and the confluence of the pulmonary arteries. Six children with congenital heart

isease born after in vitro fertilization and embryo transfer have been previously described.¹⁻³ Four patients had transposition of great arteries,^{1,2} one had ventricular septal defect,² and the last one was affected by tetralogy of Fallot.³ To our knowledge, complex congenital heart malformation such as in our case has not been reported yet. Further studies on outcomes of in vitro fertilization are needed to determine the exact incidence and types of congenital anomalies and the possible role of teratologic factors associated with this procedure.

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Hirschsprung's Disease and Ocular Autonomic Nerve Function

Purpose.—We pharmacologically assessed the ocular autonomic nervous systems of 10 children with Hirschsprung's disease, using 0.1% pilocarpine nitrate and 0.5% phenylephrine hydrochloride. Our results did not indicate any significant abnormality in the ocular autonomic nervous systems of children with Hirschsprung's disease, compared with those of normal controls.

Hirschsprung's disease is a congenital anomaly of innervation affecting the intrinsic plexuses of Auerbach and Meissner in the lower gut.¹ These autonomic plexuses are derived from the cranio-cervical neural crest.² The superior cervical ganglion (sympathetic) and the ciliary ganglion (parasympathetic) of the eye are also derived from the cranio-cervical neural crest.³

Patients and Methods.—Ten children with Hirschsprung's disease, two girls and eight boys, between 4 and 14 years of age were examined. All children had histologically proved Hirschsprung's disease. Twenty age- and sex-matched controls were obtained from our pediatric ophthalmology screening clinics.

Baseline measurements included visual acuity, orthoptic assessment, and resting pupil size, under standard conditions of brightness (luminance, 300 apostilbs). Ocular autonomic nerve function was investigated by testing for autonomic denervation

hypersensitivity of the iris. Pupil cycle measurements are unsatisfactory in the pediatric age group, in our experience. Pilocarpine, in a 0.1% solution, was used to determine the pupillary parasympathetic status, and 0.5% phenylephrine hydrochloride was used to determine its sympathetic status. Both of these drugs are direct acting and mimetic. Drug instillation was fully randomized in a double-blind manner, and normal saline solution was used as a control in the nontested eye. One drop (0.05 mL) was instilled into the lower conjunctival fornix, and 45 minutes later the pupil diameter was measured using a commercially available set of black circles, with the patient's eyes focused for distance.

At the patient's first visit 0.1% pilocarpine was placed in the conjunctival sac of one eye, and normal, sterile saline solution was placed in the conjunctival sac of the other eye. One month later the process was repeated using 0.5% phenylephrine as the active pharmaceutical agent. The children were screened for ocular evidence of von Recklinghausen's disease, Down syndrome, and Waardenburg's syndrome, all known associations of Hirschsprung's megacolon.

Results.—Our results indicated that neither 0.1% pilocarpine nor 0.5% phenylephrine cause any significant effect on pupil diameter compared with administration of normal saline solution. A positive response in denervation hypersensitivity typically results in a 3- to 4-mm change in pupil diameter.⁴ There was no significant difference between the responses of the control group compared with children with Hirschsprung's disease. Any observed difference is within the realm of experimental error and, therefore, *t* tests and confidence intervals were not indicated.

Comment.—Wilhelm first described the neural crest in 1868 and later reported the migration of these cells into spinal and cranial ganglia, including the superior cervical ganglion and ciliary ganglion of the eye. It has since been shown experimentally that the intrinsic plexuses of the colon are derived from the same cranio-cervical neural crest.³ Neuroblasts develop in the intestinal tract by cephalocaudal migration along vagal trunks through the intestine. Hirschsprung's disease is a neurocristopathy resulting from an abnormality in migration of these neural crest precursors of the myenteric plexuses.

Ocular neurocristopathies associated with Hirschsprung's megacolon are well documented and include Waardenburg's syndrome, Marcus-Gunn ptosis, and von Recklinghausen's disease.⁵ Because of these associations it was theoretically considered that

children with Hirschsprung's disease might exhibit abnormal ocular autonomic function, as the ocular autonomic nervous system develops embryologically from the same cranio-cervical neural crest as the intrinsic ganglia of the gut.

The principle of denervation hypersensitivity, defined as an increased response of a tissue to a chemical neurotransmitter or agonist and following deprivation of its nerve supply, may be applied in the assessment of ocular autonomic nerve function.⁶ Pupil diameter represents the relative balance of autonomic activity in the anterior segment of the eye; sympathetic nerves affect pupillary dilation via the dilator pupillae, and parasympathetic nerves affect pupillary constriction via the sphincter pupillae.

Little is known about testing ocular autonomic nerve function in children, but our results and clinical experience suggest that it differs little from that of adults. There were no documented local or systemic adverse reactions in any of the children tested.

Analysis of the results showed no evidence of a specific ocular autonomic neuropathy in children with Hirschsprung's disease. Further investigations may elicit nonocular neuropathy in other systems of children with Hirschsprung's disease.

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The Human Immunodeficiency Virus–Infected Infant

A Diagnostic Dilemma

Congenital infection with the human immunodeficiency virus (HIV) has a profound effect on growth and development of the newborn. As is typical for congenitally acquired infections, the symptoms in the young infant are distinct from those observed in older children and adults. Although HIV-infected infants have been stud-

See also p 1147.

ied for half a dozen years,^{1,2} and detailed descriptions of the natural course have appeared in the literature,³⁻⁵ many issues related to maternal-fetal transmission are poorly understood. In this issue of *AJDC*, Johnson and coworkers⁶ report a prospective study of 20 infants born in the Baltimore, Md, area to HIV-seropositive women. The infants were observed for a minimum of 18 months to determine the natural history of congenital HIV infection. The study fails, however, as did previous studies of congenital HIV infection, to address the maternal-fetal factors that affect virus transmission from the mother to the offspring and to take the guesswork out of diagnosing HIV infection in the very young infant.

Despite the close contact between mother and fetus in utero, the prospects of virus-loaded macrophages migrating across the placenta, and the likelihood of exposure of the infant during the birthing process to maternal blood and secretions, only 25% to 50% of the offspring of HIV-infected mothers appear to be infected by the virus. Are there some yet unknown protective mechanisms involved? On the other hand, this estimate may have to be revised because of the recent observation that HIV infection can be dormant for years without active viral replication.^{7,8} Without an animal model

to study maternal-fetal transmission, many of the more fundamental questions related to vertical transmission of HIV from the mother to the fetus cannot be answered with certainty. A number of pressing issues, however, must be addressed immediately. First, we have to find socially and legally acceptable ways to identify all HIV-seropositive pregnant women, a strategy considered essential for protecting the fetus from other sexually transmitted infectious diseases. Without identifying infants at risk, innovative steps to prevent maternal-fetal transmission cannot be taken, and optimal care of the affected infants cannot be provided. The experience from Baltimore shows that if approached in a sensitive way, pregnant women with known risk factors will consent almost without exception to HIV testing.

Second, we need to sort out the major events that play a role in the transfer of HIV from the mother to the fetus. Human immunodeficiency virus has been cultured from fetal tissue at as early as 8 weeks of gestation,⁹ suggesting that at least some fetuses are exposed to HIV during early pregnancy. Little is known about the placenta as a barrier between the maternal and fetal circulation, and many questions remain as to the importance of an active transport across the placenta. Can free virus penetrate or directly infect the syncytiotrophoblast? Do HIV-infected macrophages or CD4⁺ lymphocytes actively cross the placenta? Can virus cross the placenta by forming complexes with specific antibody that binds via the Fc receptors to phagocytic cells? How frequent and how important are maternal-fetal transfusions at the time of delivery?

A third area that needs to be addressed concerns maternal factors that may play a role in vertical trans-

mission of HIV. Offspring of women with high antibody titers to gp120 have a lower incidence of infection than offspring of women with depressed levels.¹⁰ It has been proposed—but not documented—that free virus in the maternal circulation facilitates vertical transmission of HIV to the fetus.

Last, and most important, we have not yet developed the skills to clearly differentiate between infected and noninfected offspring of HIV-seropositive mothers. New diagnostic methods are urgently needed. The presence of maternally derived HIV-specific antibody in the infant's blood makes interpretation of serologic assays difficult. It may take up to 15 months for passively acquired antibodies to disappear from the infant's circulation, too long a wait for the parents and the infant's physician. The observation that some HIV-infected infants never produce antibody to HIV makes it even more difficult to interpret the results of antibody testing.

Promising new techniques designed to detect the virus or to assess the infant's own immune response to HIV have been introduced and tested in small pilot studies. Quantitative analysis of serum antibodies to HIV suggests infection of the infant if the initial drop in antibody titer after birth is followed by a persistent rise. Similarly, the appearance of new bands in serially tested serum using Western blot analysis, the detection of HIV-specific IgM or IgG subclass antibody not present in maternal serum,¹¹ or the demonstration of *in vitro* synthesis of HIV-specific antibody by peripheral blood lymphocytes from infants at risk¹² may signal a specific immune response by the infant and indicate infection with HIV. A positive culture, a technique limited to major medical centers, is considered the gold standard for confirming the diagnosis.

of HIV infection. The success rate for obtaining positive cultures from HIV-infected infants varies and depends on the experience of the investigators, the type of cell line used in the co-culture system, and the number of infective viral particles placed in the culture system. Under optimal conditions, more than 90% of seropositive older children and adults turn out to be culture positive; the success rate in infants may be less. Amplification of part of the HIV genome by the polymerase chain reaction followed by hybridization with a specific probe appears to be a most promising technique for rapid and highly specific detection of early HIV infection in the neonate.^{13,14} However, at present, only a few laboratories have the experience to appropriately interpret the results. Broad use of these new techniques will be vital for early diagnosis, systematic evaluation of new antiviral drugs, and,

finally, the prevention of maternal-fetal transmission of HIV.

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Perinatal Asphyxia and Cerebral Palsy

Fact, Fiction, or Legal Prediction?

The scenario is familiar to all of us. A medical malpractice lawsuit has been filed on behalf of a child with cerebral palsy. An obstetrician and often the pediatrician who cared for the child at birth and many years hereafter receive court documents naming them as defendants in the suit.

See also p 1154.

The child may be several years old now and suffers from a visible and distressing physical condition. The plaintiff's attorney sorts through medical records with a fine-tooth comb looking for any potential impropriety, searching for fault in the mother's or child's medical treatment. The job of the plaintiff's attorney is to show that medical care rendered to the mother and/or infant fell "below accepted standards of care" and "to a medical probability" contributed to the child's

current medical condition.

The logic of this legal case often rests on the association of perinatal events to long-term neurologic sequelae such as cerebral palsy. However, there is an increasing body of medical knowledge bringing down the time-honored belief that catastrophic events surrounding the perinatal period lead to cerebral palsy. The work of Naeye et al,¹ published in this issue of *AJDC*, provides ongoing strong evidence that cerebral palsy is not the result of perinatal asphyxial events in the full-term infant, but the consequence of usually unpreventable prenatal intrauterine problems.

Cerebral palsy is a general descriptive term referring to a nonprogressive motor deficit of early onset. The specific type (spastic diplegic/quadruplegic, choreoathetoid, dystonic) is determined by the location of the lesions within the central nervous system and timing of its occurrence.²

When Little³ described this disorder in 1862, he was certain that the origins of the problems he found were related to the birthing process. Histories of prolonged labor, breech presentations, and premature birth were commonly found in children with "spastic rigidity." Many children presented with delayed onset of respirations, convulsions, and coma. However, a conflicting view was provided by Freud⁴ in his early career as a neurologist. In a monograph in 1897, he stated that

since the abnormal process of birth frequently produces no effect, one cannot exclude the possibility that, despite Little's anamnesis, diplegia still might be of congenital origin. Difficult birth in itself in certain cases is merely a symptom of deeper effects that influenced the development of the fetus.

For many years, it was believed that one of the complications of a breech birth was cerebral palsy. However, it

is now recognized that there is a higher incidence of abnormalities in fetuses found in a breech presentation.⁵ Abnormalities of labor and delivery may constitute markers rather than causes of brain damage. Thus, in many cases of cerebral palsy, it is probable that preexisting brain damage resulted in intrapartum neonatal asphyxia rather than the converse. Now, nearly 100 years later, we are at the forefront of realizing the truth and soundness of Freud's statement!

Utilizing data from the Collaborative Perinatal Study of the National Institute of Neurological and Communicative Disorders and Stroke, Bethesda, Md,⁶ Naeye et al sought to determine what role birth asphyxia plays in the development of cerebral palsy in full-term infants, and to ascertain whether disorders of intrauterine origin may manifest as cerebral palsy. The collaborative Perinatal Study followed the course of nearly 60 000 pregnancies in 12 medical school-affiliated hospitals from 1959 to 1966 in a careful prospective fashion. Although newer, precise methods of assessing favorability of the intrauterine environment (electronic fetal monitoring, pH sampling) were not in use then, indicators studied in the Collaborative Perinatal Study, such as neonatal seizures, time until the onset of respiration, and fetal bradycardia, are still valid indicators of a potentially hostile intrauterine environment. He found that birth asphyxia accounted for only 6% of the cases of cerebral palsy. Congenital disorders could be identified as a cause of cerebral palsy in many more cases of quadriplegic cerebral palsy than birth asphyxia. Naeye et al conclude that it is unlikely that state-of-the-art obstetric and pediatric managements could have prevented the cerebral palsy in these full-term infants since most of the disorders that damaged their brains occurred long before labor and delivery, and thus were unrecognized at the time the brain damage occurred.

Numerous studies have criticized the causal relationship of birth asphyxia and cerebral palsy on the presence of fetal distress and low Apgar scores.^{7,8} (I am sure that Dr Virginia Apgar never intended for her rapid,

numerical assessment of an infant's adaptation to extrauterine life to be used as a means for determining neurologic outcome!) To state that cerebral palsy was caused by birth asphyxia requires objective proof of a profoundly disturbed intrauterine environment, such as blood gas evidence of severe acidosis, hypoxia, and hypercarbia. In addition, there should be postnatal evidence of neurologic impairment (seizures, apnea, tone abnormalities) and other organ-system compromise, such as renal insufficiency and cardiovascular embarrassment. There must also be no evidence that a nonasphyxial condition was present that could have caused the cerebral palsy. Naeye et al¹ and Nelson and Ellenberg⁸ found that congenital malformations (hydrocephalus, microcephaly, etc) could explain many times more cases of cerebral palsy than did birth asphyxia. Yet, perhaps most important, is the discovery that no cause could be identified for the majority of cases of cerebral palsy in term infants. Nelson and Ellenberg concluded in their study of predictive factors of cerebral palsy that "we probably do not know what causes most cases of cerebral palsy." However, prematurity and low birth weight are strong risk factors for cerebral palsy.⁸ Prevention of preterm delivery would be a tremendous stride in preventing cerebral palsy.

What does all this mean for our obstetric colleagues? We must be prudent and exact in our medical documentation of infants with a complicated adaptation to extrauterine life. When an infant is born with Apgar scores of 2 and 5 at 1 and 5 minutes, respectively, we should not write in the chart an assessment of perinatal asphyxia (unless there is objective biochemical evidence to support this!). Perinatal asphyxia is a symptom complex indicative of an underlying pathophysiologic process. *Perinatal depression* may be a more appropriate descriptive term that does not point accusatory fingers at other health care providers. Few studies have shown that a poor neurodevelopmental outcome is the result of "substandard" obstetric care. As pointed out by Niswander et al,⁹ "fetal distress may oc-

casionally be followed by brain damage, but the obstetrician can seldom interrupt that relationship."

What is the role of the pediatrician in controlling the unchecked proliferation of obstetric malpractice suits? We must not ascribe apparent brain damage to intrapartum causes. We must carefully educate attorney (plaintiff and defense) and the public at-large that whenever there is a bad outcome, someone is not always to blame. We must dispel the plaintiff attorney's claim that intrapartum asphyxia causes brain damage. As more data are accumulated, the scientific verdict will be that perinatal asphyxia rarely leads to cerebral palsy or brain injury. The theory of perinatal acquisition of brain damage has a element of fiction and legal prediction. Preconceived ideas about the origin of cerebral palsy need stringent reassessment. Rather than nonscientific speculation on the origins of brain damage fanning the flames of the obstetric malpractice litigation fire, we should concentrate on "just the facts, ma'am, just the facts."

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Leads From the MMWR

Morbidity and Mortality Report
Centers for Disease Control, Atlanta

Recommendations of the Immunization Practices Advisory Committee (ACIP) Mumps Prevention

THIS REVISED Immunization Practices Advisory Committee (ACIP) recommendation on mumps vaccine updates the 1982 recommendation.

MUMPS VIRUS VACCINE

Mumps virus vaccine is prepared in chick-embryo cell culture. The vaccine produces a subclinical, noncommunicable infection with very few side effects. Mumps vaccine is available both in monovalent (mumps only) form and in combinations: mumps-rubella and measles-mumps-rubella (MMR) vaccines.

The vaccine is approximately 95% efficacious in preventing mumps disease; greater than 97% of persons known to be susceptible to mumps develop measurable antibody following vaccination. Vaccine-induced antibody is protective and long-lasting, although of considerably lower titer than antibody resulting from natural infection. The duration of vaccine-induced immunity is unknown, but serologic and epidemiologic data collected during 20 years of live vaccine use indicate both the persistence of antibody and continuing protection against infection. Estimates of clinical vaccine efficacy ranging from 75% to 95% have been calculated from data collected in outbreak settings using different epidemiologic study designs.

Vaccine Shipment and Storage

Administration of improperly stored vaccine may fail to protect against mumps. During storage before reconstitution, mumps vaccine must be kept at 2-8 C (35.6-46.4 F) or colder. It must also be protected from light, which may inactivate the virus. Vaccine must be shipped at 10 C (50 F) or colder and may be shipped on dry ice.

After reconstitution, the vaccine should be stored in a dark place at 2-8 C (35.6-46.4 F) and discarded if not used within 8 hours.

VACCINE USAGE

General Recommendations

Susceptible children, adolescents, and adults should be vaccinated against mumps, unless vaccination is contraindicated. Mumps vaccine is of particular value for children approaching puberty and for adolescents and adults who have not had mumps. MMR vaccine is the vaccine of choice for routine administration. Persons should be considered susceptible to mumps unless they have documentation of (1) physician-diagnosed mumps, (2) adequate immunization with live mumps virus vaccine on or after their first birthday, or (3) laboratory evidence of immunity. Because live mumps vaccine was not used routinely before 1977 and because the peak age-specific incidence was in 5-9-year-olds before the vaccine was introduced, most persons born before 1957 are likely to have been infected naturally between 1957 and 1977. Therefore, they generally may be considered to be immune, even if they may not have had clinically recognizable mumps disease.

Persons who are unsure of their mumps disease history and/or mumps vaccination history should be vaccinated.

Age. Live mumps virus vaccine is recommended at any age on or after the first birthday for all susceptible persons, unless a contraindication exists.

Persons Exposed to Mumps

Use of Vaccine. When given after exposure to mumps, live mumps virus

vaccine may not provide protection.

Use of Immune Globulin. Immune globulin (IG) has not been demonstrated to be of established value in postexposure prophylaxis and is not recommended.

Adverse Effects of Vaccine Use

In field trials before licensure, illnesses did not occur more often in vaccinees than in unvaccinated controls. Reports of illnesses following mumps vaccination have mainly been episodes of parotitis and low-grade fever. Allergic reactions including rash, pruritus, and purpura have been temporally associated with mumps vaccination but are uncommon and usually mild and of brief duration.

Contraindications to Vaccine Use

Pregnancy. Although mumps vaccine virus has been shown to infect the placenta and fetus, there is no evidence that it causes congenital malformations in humans. However, because of the theoretical risk of fetal damage, it is prudent to avoid giving live virus vaccine to pregnant women.

Severe Febrile Illness. Vaccine administration should not be postponed because of minor or intercurrent febrile illnesses, such as mild upper respiratory infections.

Allergies. Because live mumps vaccine is produced in chick-embryo cell culture, persons with a history of anaphylactic reactions (hives, swelling of the mouth and throat, difficulty breathing, hypotension, or shock) after egg ingestion should be vaccinated only with caution using published protocols.

Since mumps vaccine contains trace amounts of neomycin (25 µg), persons who have experienced anaphylactic re-

actions to topically or systemically administered neomycin should not receive mumps vaccine.

Recent IG Injection. Passively acquired antibody can interfere with the response to live, attenuated-virus vaccines. Therefore, mumps vaccine should be given at least 2 weeks before the administration of IG or deferred until approximately 3 months after the administration of IG.

Altered Immunity. In theory, replication of the mumps vaccine virus may be potentiated in patients with immune deficiency diseases and by the suppressed immune responses that occur with leukemia, lymphoma, or generalized malignancy or with therapy with corticosteroids, alkylating drugs, antimetabolites, or radiation. In general, patients with such conditions should not be given live mumps virus vaccine. Because vaccinated persons do not transmit mumps vaccine virus, the risk of mumps exposure for those patients may be reduced by vaccinating their close susceptible contacts.

An exception to these general recommendations is in children infected with human immunodeficiency virus (HIV); all asymptomatic HIV-infected children should receive MMR at 15 months of age. If measles vaccine is administered to symptomatic HIV-infected children, the combination MMR vaccine is generally preferred.

Patients with leukemia in remission whose chemotherapy has been terminated for at least 3 months may also receive live mumps virus vaccine. Short-term (less than 2 weeks' duration) corticosteroid therapy, topical steroid therapy (e.g., nasal, skin), and intraarticular, bursal, or tendon injection with corticosteroids do not contraindicate mumps vaccine administration. However, mumps vaccine should be avoided if systemic immunosuppressive levels are reached by prolonged, extensive, topical application.

Other. There is no known association between mumps vaccination and pancreatic damage or subsequent development of diabetes mellitus.

MUMPS CONTROL

The principal strategy to prevent mumps is to achieve and maintain high immunization levels, primarily in infants and young children. Universal immunization as a part of good health care should be routinely carried out in physicians' offices and public health clinics. Programs aimed at vaccinating

children with MMR should be established and maintained in all communities. In addition, all other persons thought to be susceptible should be vaccinated unless otherwise contraindicated. This is especially important for adolescents and young adults in light of the recently observed increase in risk of disease in these populations.

Because access to some population subgroups is limited, the ACIP recommends taking maximal advantage of clinic visits to vaccinate susceptible persons greater than or equal to 15 months of age by administering MMR, diphtheria-tetanus-pertussis (DTP), and oral polio vaccine (OPV) simultaneously if all are needed. Health agencies should take necessary steps, including the development, adoption, and enforcement of comprehensive immunization requirements, to ensure that all persons in schools at all grade levels and in day-care settings are protected against mumps. Similar requirements should be considered for colleges, as recommended by the American College Health Association,²⁵ and selected places of employment where persons in this age cohort are likely to be concentrated or where the consequences of disease spread may be more severe (e.g., medical-care settings).

In determining means to control mumps outbreaks, exclusion of susceptible students from affected schools and schools judged by local public health authorities to be at risk for transmission should be considered. Such exclusion should be an effective means of terminating school outbreaks and quickly increasing rates of immunization. Excluded students can be readmitted immediately after vaccination. Pupils who have been exempted from mumps vaccination because of medical, religious, or other reasons should be excluded until at least 26 days after the onset of parotitis in the last person with mumps in the affected school. Experience with outbreak control for other vaccine-preventable diseases indicates that almost all students who are excluded from the outbreak area because they lack evidence of immunity quickly comply with requirements and can be readmitted to school.

MUMPS DISEASE SURVEILLANCE AND REPORTING OF ADVERSE EVENTS

There is a continuing need to improve the reporting of mumps cases

and complications and to document duration of vaccine effectiveness. Thus, for areas in which mumps reportable disease, all suspected cases of mumps should be reported to or state health officials.

The National Childhood Vaccine Injury Compensation Program established by the National Childhood Vaccine Injury Compensation Act of 1986 requires physicians and other health care providers who administer vaccines to maintain permanent immunization records and to report occurrences of certain adverse events to the U.S. Department of Health and Human Services. Reporting and reporting requirements took effect March 21, 1988. Reportable adverse events include those listed in the Code of Federal Regulations for mumps²⁶ and events specific to the manufacturer's vaccine package insert as contraindications to further doses of mumps vaccine.

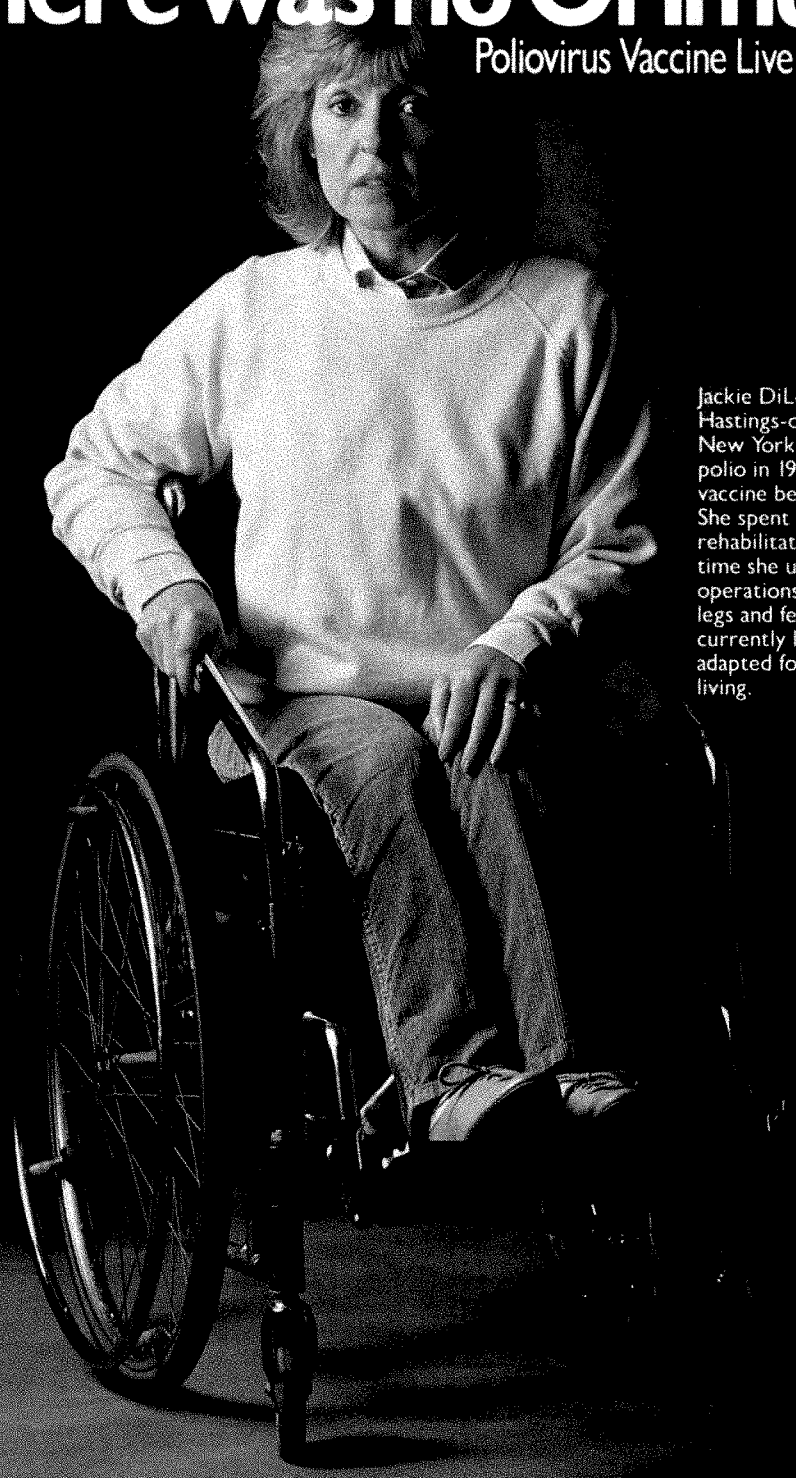
Although there eventually will be one system for reporting adverse events following immunizations, separate systems currently exist. Appropriate reporting methods currently depend on the source of funding used to purchase the vaccine. Events that occur after receipt of vaccine purchased with public funds, federal, state, and/or local government funds must be reported by the administering health provider to the appropriate local, county, or state health department. The state health department completes and submits the report forms to CDC. Reportable events that follow administration of vaccine purchased with private money are reported by the health-care provider directly to the Food and Drug Administration.

RECOMMENDATIONS FOR INTERNATIONAL TRAVEL

Mumps is still endemic throughout most of the world. While vaccination against mumps is not a requirement for entry into any country, susceptible children, adolescents, and adults would benefit by being vaccinated with a single dose of vaccine (usually as MMR), unless contraindicated before beginning travel. Because of concern about inadequate seroconversion due to persisting maternal antibody and because the risk of serious disease from mumps infection is relatively low for persons less than 12 months of age, a vaccine need not be given mumps vaccine before travel. (*MMWR* vol 38, No.

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A Brief Summary

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INDICATIONS: For prevention of poliomyelitis caused by Poliovirus Types 1, 2, and 3.

CONTRAINDICATIONS: Under no circumstances should this vaccine be administered parenterally.

Administration of the vaccine should be postponed or avoided in those experiencing any acute illness and in those with any advanced debilitated condition or persistent vomiting or diarrhea.

ORIMUNE must not be administered to patients with immune deficiency disease such as combined immunodeficiency, hypogammaglobulinemia, and agammaglobulinemia. Further, ORIMUNE must not be administered to patients with altered immune states, such as those occurring in thymic abnormalities, leukemia, lymphoma, or generalized malignancy or by lowered resistance from therapy with corticosteroids, alkylating drugs, antimetabolites, or radiation. ORIMUNE should not be given to members of a household in which there is a family history of immunodeficiency until the immune status of all members is determined to be normal. All persons with altered immune status should avoid close household-type contact with recipients of the vaccine for at least six to eight weeks. Inactivated poliovirus vaccine (IPV) is preferred for immunizing all persons in the above described circumstances.

WARNINGS: Under no circumstances should this vaccine be administered parenterally.

Administration of the vaccine should be postponed or avoided in those experiencing any acute illness and in those with any advanced debilitated condition or persistent vomiting or diarrhea.

Other viruses (including poliovirus and other enteroviruses) may interfere with the desired response to this vaccine, since their presence in the intestinal tract may interfere with the replication of the attenuated strains of poliovirus in the vaccine.

PRECAUTIONS: Preliminary data indicate that immune globulin (Human) (IG) does not appear to interfere with immunization with poliovirus vaccine live oral trivalent (OPV). However, until more data are available, it would seem prudent not to administer OPV shortly after IG, unless such a procedure is unavoidable, for example, with unexpected travel to or contact with epidemic areas or endemic areas. If OPV is given with or shortly after IG, the dose should probably be repeated after three months if immunization is still indicated.

The vaccine is not effective in modifying or preventing cases of existing and/or incubating poliomyelitis.

NATIONAL CHILDHOOD VACCINE INJURY ACT OF 1986 (as amended in 1987)

Manufacturer and lot number of vaccine administered must be recorded by health care provider in vaccine recipient's permanent record, along with date of administration and name, address, and title of person administering vaccine.

Health care provider must report to a health department or to the FDA the occurrence of any event set forth in the Vaccine Injury Table including: paralytic poliomyelitis—in a nonimmunodeficient recipient within 30 days of vaccination—in an immunodeficient recipient within 6 months of vaccination; any vaccine-associated community case of paralytic poliomyelitis; or any acute complication or sequela (including death) of above even if the vaccine is not used.

Use in Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Poliovirus vaccine live oral trivalent. It is also not known whether OPV can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Although there is no convincing evidence documenting adverse effects of either OPV or IPV on the developing fetus or pregnant woman, it is prudent on theoretical grounds to avoid vaccination of pregnant women. However, if immediate protection against poliomyelitis is needed, OPV is recommended. (See **CONTRAINDICATIONS** and **ADVERSE REACTIONS**.)

ADVERSE REACTIONS: Paralytic disease following the ingestion of live poliovirus vaccines has been, on rare occasion, reported in individuals receiving the vaccine (see, for example, **CONTRAINDICATIONS**), and in persons who were in close contact with vaccinees. The vaccine viruses are shed in the vaccinee's stools for at least six to eight weeks as well as via the pharyngeal route. Most reports of paralytic disease following ingestion of the vaccine or contact with a recent vaccinee are based on epidemiological analysis and temporal association between vaccination or contact and the onset of symptoms. Most authorities believe that a causal relationship exists. Prior to administration of the vaccine, the attending physician should warn or specifically direct personnel acting under his authority to convey the warning: the vaccinee, parent, guardian, or other responsible person of the possibility of vaccine-associated paralysis, particularly to susceptible family members and other close personal contacts.

The Centers for Disease Control report that during the years 1973 through 1984 approximately 274.1 million OPV doses were distributed in the US. During this period, 105 vaccine-associated cases were reported (1 case per 2.6 million doses distributed). Of these 105 cases, 35 occurred in vaccine recipients (1 case per 7.8 million doses distributed), 50 occurred in household and nonhousehold contacts of vaccinees (1 case per 5.5 million doses distributed), 14 occurred in immunodeficient recipients or contacts, and 6 occurred in persons with no history of vaccine exposure, from whom vaccine-like viruses were isolated.

Thirty-three (94%) of the recipient cases, 41 (82%) of the contact cases, and 5 (36%) of the immunodeficient cases were associated with the recipient's first dose of OPV. Because most cases of vaccine-associated paralysis have occurred in association with the first dose, the CDC has estimated the likelihood of paralysis in association with first v subsequent doses of OPV, using the number of births during 1973-1984 to estimate the number of first doses distributed, and subtracting this from the total distribution to estimate the number of subsequent doses distributed. This method estimates a frequency of paralysis for recipients of 1 case per 1.2 million first doses v 1 case per 116.5 million subsequent doses; for contacts one case per 1 million first doses v 25.9 million subsequent doses; with an overall frequency of 1 case per 520,000 first doses v 1 case per 12.3 million subsequent doses.

Other methods of estimating the likelihood of paralysis in association with OPV have been described. Because the number of susceptible vaccine recipients or contacts of recipients is not known, the true risk of vaccine-associated poliomyelitis is impossible to determine precisely.

When the attenuated vaccine strains are to be introduced into a household with adults who have not been adequately vaccinated or whose immune status cannot be determined, the risk of vaccine-associated paralysis can be reduced by giving the adults one dose of IPV per month for three months before the children receive Poliovirus vaccine live oral trivalent ORIMUNE. The children may receive the first dose of ORIMUNE at the same visit that the adult receives the third dose of IPV. The CDC reports that no paralytic reactions to IPV are known to have occurred since the 1955 cluster of poliomyelitis cases caused by vaccine that contained live polioviruses that had escaped inactivation.

The ACIP states: "Because of the overriding importance of ensuring prompt and complete immunization of the child and the extreme rarity of OPV-associated disease in contacts, the Committee recommends the administration of OPV to a child regardless of the poliovirus-vaccine status of adult household contacts. This is the usual practice in the United States. The responsible adult should be informed of the small risk involved. An acceptable alternative, if there is a strong assurance that ultimate, full immunization of the child will not be jeopardized or unduly delayed, is to immunize adults according to the schedule outlined above before g OPV to the child."

The ACIP has concluded that "Oral polio vaccine remains the vaccine of choice for primary immunization of children."

Rev.



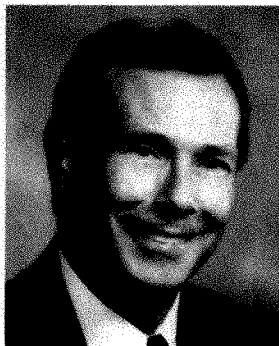
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The Editorial Board Speaks . . .

William B. Strong, MD



Bill Strong has an enviable academic record. Entering the 1989-1990 academic year, he has published more than 200 articles, book chapters, and self-instructional materials. His research efforts have been strong, with more than \$2 million in extramural support. He has been most active in investigation of physical activity and nutrition in relation to cardiovascular disease. He has also been recognized locally, regionally, and nationally as an outstanding educator. Bill's service activities, apart from his editorship of the SPORTS MEDICINE section of *AJDC*, include chairmanship and membership on multiple national pediatric and cardiovascular committees. He has been on the faculty of the Medical College of Georgia, Augusta, for the past 20 years, and is currently professor of pediatrics and director of pediatric cardiology. Bill is married to Lynthia and they have six children, ranging in age from 19 to 28 years.

YOU ARE A PREVENTIVE CARDIOLOGIST: THE SCOPE OF PEDIATRIC PREVENTIVE CARDIOLOGY

The excitement of pediatric preventive cardiology arises from its magnitude. When one becomes involved in the practice of preventive cardiology, its relationship to general good health becomes self-evident. You have been trained as preventive cardiologists. Until now you have just not focused your activities on an organ system. Historically, pediatricians' natural bailiwick has been preventive medicine and public health. Pediatricians have always been interested in childhood nutrition; they have led the good fight against smoking and have encouraged children to be physically active. Prudent diet, physical activity, and nonsmoking are the pillars of the practice of preventive cardiology. The only difference between what pediatricians did and are beginning to do under the rubric of preventive cardiology is that they are now targeting their advocacy on an organ disease process.

The prevention or deferment of the symptomatic phase of chronic disease is dependent on the teaching and implementation of healthy life-styles early in life and reinforcing them at all appropriate encounters, ie, prenatally and during the first year of life, early childhood, late childhood, and adolescence. At each of these stages, messages for healthy behaviors should be provided to the child and parents. At each visit, the message should be appropriate to the age of the child and circumstance of the encounter. The approach to nonsmoking recommended by Perry and Silvis¹ is an excellent example of age- and encounter-specific guidelines.

Two major strategies in the prevention of adult-onset coronary artery disease and hypertension are available to the pediatrician: the high-risk approach and the community (population, public health) strategy. The high-risk approach identifies individuals at highest risk of future disease by some set of characteristics and targets these individuals for aggressive interventional strategies. Because of the phenomenon of tracking, this method of identification will affect the 5% to 10% at greatest risk for future disease. However, since one half the population is at risk for future disease, primary prevention also should be applied to the population as a whole. Because of the great prevalence of disease in the population,

the community approach believes that certain intervention should be recommended for the entire population, eg, prudent diet, nonsmoking, and regular physical activity. These are not very radical strategies. They encompass what most pediatricians recommend.

Most pediatric preventive cardiologists would support combination of community and high-risk strategies. The preventive pediatric cardiologist would suggest the community strategy plus an aggressive search for individuals at high risk because of their family history and/or elevated total cholesterol and low-density lipoproteins cholesterol levels.

Because only one half of youngsters with significantly elevated cholesterol levels (≥ 5.2 mmol/L) will have a positive family history, cholesterol screening of all children should be performed in the pediatrician's office.² The American Heart Foundation has presented a cogent argument for universal screening of all children prior to school entry. When serum cholesterol level is elevated, validation of the office test with lipoprotein profile will enable the pediatrician to identify children whose values are excessive.

Experience suggests that the young to middle-aged parent(s) of these children also will have elevated levels. The majority of these adults are unaware of their values. Approaching preventive cardiology as a family affair is crucial to compliance. What parents are not more likely to try to change their own life-styles when they are aware that it is in the best interest of their child?

Measurement of the child's cholesterol levels provides the pediatrician an excellent entrée into a discussion of the importance of good nutrition, the benefits of physical activity, and the importance of nonsmoking. Today parents want the child's pediatrician to be interested in good health and wellness. It is in everyone's best interest.

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Natural History and Serologic Diagnosis of Infants Born to Human Immunodeficiency Virus–Infected Women

John P. Johnson, MD; Prasanna Nair, MD; Susan E. Hines, MS, CPNP; Sue W. Seiden, MS, CPNP; Lindsay Alger, MD; Daniel R. Revie; Kathleen M. O'Neil, MD; Richard Hebel, PhD

• Perinatal transmission of human immunodeficiency virus is thought to occur in 25% to 50% of the offspring of infected women. Standard diagnostic methods do not permit identification of the infected newborns. To assess diagnostic methods and document the natural history of perinatal human immunodeficiency virus infection, 20 children born to human immunodeficiency virus–infected women were followed prospectively for 18 months by measuring antibody titer, Western blot profiles, and antigenemia, and the results were compared with clinical outcome. Endogenous synthesis of anti-human immunodeficiency virus IgG was demonstrated in 6 of the 8 infected children. Four children synthesized IgM against human immunodeficiency virus. Five had demonstrable p24 antigenemia. No significant differences between infected and noninfected children were noted at birth except drug withdrawal, which occurred more frequently in noninfected infants. The incidence of adenopathy, hepatomegaly, and neurologic and immunologic abnormalities in the infected children were compared with noninfected children. The distinguishing illnesses were the opportunistic infections, lobar pneumonia, and failure to thrive. Seven of the 8 infected children had human immunodeficiency virus–mediated disease by 1 year of age (Centers for Disease Control [Atlanta, Ga] P2 classification), and four had acquired immunodeficiency syndrome (Centers for Disease Control P2D). These studies offer an approach to diagnosis of human immunodeficiency virus infection in infants and document the natural history and possible outcomes of infected children. (AJDC. 1989;143:1147-1153)

In 1983, the first evidence of acquired immunodeficiency syndrome (AIDS) in infants was presented.^{1,2} Since that time, the number of pediatric AIDS cases has grown rapidly to over 1300.³ There are many more children who have human immunodeficiency virus (HIV) infection with milder disease or no apparent disease.^{4,6} The Centers for Disease Control, Atlanta, Ga, have recommended the establishment of obstetric screening programs to prospectively identify infants with perinatal exposure to HIV.⁷ Appropriate counseling and health planning is complicated by uncertainties regarding diagnosis of HIV infection in infancy and the lack of prospective data regarding the natural history and outcome of HIV infection in infants.

For editorial comment see p 1138.

The major difficulty in diagnosis of HIV infection in infants results from placental transfer of maternal IgG to the fetal circulation, thereby preventing accurate diagnosis by routine enzyme-linked immunosorbent assay or Western blot. It has been estimated that 15 months are required before demonstration of antibody against HIV indicates infant infection.⁸ Recent evidence suggests that diagnosis in infants may be even more difficult because of delayed or absent synthesis of anti-HIV antibody in infected children.⁹⁻¹¹ Furthermore, no prospective assessment of other diagnostic methods (ie, IgM synthesis or antigen detection) for HIV infection are available.

It is uncertain what proportion of the infected pediatric population will develop AIDS or other HIV-mediated diseases, but this proportion is thought to be high.^{5,12} It has become clear that

there is a wide spectrum of presentations of HIV-mediated disease in children, including recurrent or unusual infections, neurologic disease, the wasting syndrome, and hematologic disorders.¹³⁻¹⁶

Lacking, however, is the detailed natural history data necessary for appropriate health maintenance, disease recognition, and early intervention. In this article, we present a prospective longitudinal study of the diagnostic, clinical, and laboratory findings in 20 children born to HIV-infected women. A variety of methods to document HIV infection have been studied. The age at onset of the signs and symptoms of HIV infection in infants is also documented. Evidence is presented that the majority of infected children (ie, 88%) will develop disease manifestations (Centers for Disease Control P2 classification) by 1 year of age—confirming the marked susceptibility of infants to HIV infection and the pressing need for interventional strategies.

PATIENTS AND METHODS Enrollment

All women presenting to the University of Maryland, Baltimore, obstetric service between September 1985 and March 1986 were screened for risk factors for HIV infection by written questionnaire. Women who identified a risk factor for HIV infection were then asked to participate in a study of AIDS risk for themselves and their children. Informed consent was obtained both for participation in the study and for HIV antibody testing in mother and child. All women who identified a risk factor for HIV infection agreed to participate in this study. Approximately 25% of these "at-risk" women were HIV seropositive. Ninety percent of the mothers were black with a mean age of 28.5 years, 80% were multiparous, and 50% continued to abuse drugs during pregnancy. None had AIDS.

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Table 1.—Diagnostic, Clinical, and Laboratory Summary of HIV-Infected Children*

Laboratory Findings														Centers for Disease Control Classification			
Diagnosis				Abnormal Clinical Findings				CD4	CD4	Hyper-							
Case	IgG Inc	New Bands	IgM	Anti-gen	Skin	Adenop-athy	Neurop-athy	Spleen	Hepato-megaly	CD8 <1	Cells <800	gamma globu-linemia	4 mo	6 mo	12 mo	18 mo	
1	2	...	2	4	...	11	...	12	P1A	P1A	P2A	P2A	
2	22	...	0	...	4	P1A	P1A	P1A	P1A	
3	4	4	2	4	3	2	8	18	...	4	P1B	P2A	P2A	P2A,C	
4	4	2	2	2	...	2	...	3	4	2	P2A,D	P2A,D	P2A,D	P2A,D	
5	11	2	3	18	2	2	2	...	4	P1B	P2A	P2A	P2A	
6	5	...	4	4	9	4	2	7	9	6	9	4	P2A,B,D	P2A,B,D	P2A,B,C,D	P2A,B,C,D	
7	...	4	...	0	3	2	2	6	9	8	6	6	P2A	P2A,B,D	
8	5	3	1	1	4	3	3	12	8	8	P1A	P2A	P2D	...	

*Number indicates month of age at first documentation of abnormalities. Some variation may be noted between age of onset and Centers for Disease Control (Atlanta, Ga) classification because of requirement for persistence and/or progression of abnormality. HIV indicates human immunodeficiency virus; Inc, increase.

Assessment

The offspring of the first 20 seropositive women were evaluated at birth, and at 2, 4, 6, 9, 12, and 18 months. Maternal risk factors were intravenous drug use (90%) and sexual partner of a drug user (10%). Children were assessed by two of three practitioners at each visit who had no knowledge of laboratory results of HIV diagnostic research procedures. Physical examination data were recorded on a precoded sheet for consistency in observation. None of the children were breast-fed and none received prophylactic medications. Physical findings were considered significant only if recorded at two separate visits. Adenopathy was defined as palpable nodes greater than 0.5 cm at two or more noncontiguous nonbilateral locations. Splenomegaly was diagnosed if the examiner could palpate a spleen tip below the left costal margin. Hepatomegaly was defined as a palpable liver more than 2 cm below the right costal margin. Hyperreflexia was diagnosed if reflexes were scored 3+ on a scale of 4+.

Blood was drawn at each visit. For serum studies, the blood was allowed to clot for 30 minutes at room temperature and centrifuged at 1500g for 10 minutes. The serum was frozen at -20°C and saved for later batch assay. T-cell subsets were analyzed using fresh heparinized blood by flow cytometry on a Coulter EPICS Profile (Coulter Electronics Co, Hialeah, Fla) using T-cell subset specific monoclonal antibodies purchased from Coulter. Total serum immunoglobulin values were determined by nephelometry (Beckman Instrument Corp, Palo Alto, Calif). Hypogammaglobulinemia and hypergammaglobulinemia were defined as values of less than or greater than 2 SDs from age-defined normal ranges, respectively.

Serologic Analysis

Antibody Titer.—Antibody titer against HIV was estimated using the DuPont

HTLV-III enzyme-linked immunosorbent assay according to the manufacturers' instructions (EI DuPont de Nemours, Wilmington, Del). The optical density from this assay is roughly proportional to the amount of anti-HIV antibody in the specimen according to the manufacturer.

Western Blot Analysis.—Western blotting for anti-HIV antibody was run using the kit developed by Biotech Research Laboratories, Rockville, Md, for EI DuPont de Nemours. Each sample was incubated overnight at room temperature with a nitrocellulose strip onto which sodium dodecylsulfate-separated HIV/H9 proteins had been electrotransferred. Twenty microliters (IgG detection) or 40 µL (IgM detection) of patient serum was diluted in 2 mL of blotting buffer containing TRIS-buffered saline solution, 5% goat serum, and 5% nonfat dry milk. Bound antibody was detected using biotinylated goat antihuman IgG (δ) or IgM (µ) followed by horseradish peroxidase-conjugated avidin. Bands were developed using diaminobenzidine. Reactive samples, appearing as brown bands, were compared with positive control sera. Samples were scored as positive by the criteria established by the Consortium for Retrovirology Serology Standardization.¹⁷ Samples were considered positive if bands were detected against p24 or p31 and gp41 or gp120/160. The presence of rheumatoid factor in the sera was ruled out using the Rheumatex assay (Wampole Diagnostics, Cranberry, NJ).

Antigen Assay.—Assay for viral antigen was performed using the kit developed by Abbott Laboratories (North Chicago, Ill) according to the manufacturers' instructions. This kit is primarily sensitive for detection of p24 antigen of HIV.

Statistical Analysis.—Data were analyzed using a two-tailed Student *t* test and a *z* test for comparison of rates of occurrence per child per year.¹⁸

RESULTS HIV Diagnosis

A diagnostic and clinical summary is presented in Table 1. Using a variety of methods, a total of 17 positive assays could be documented in 8 of the 20 children.

Anti-HIV antibody levels depicted in Fig 1 (top) show the relative anti-HIV antibody amount in the five children who demonstrated an increase during the first year of life. Figure 1 (bottom) demonstrates the patterns from three children who had decreasing anti-HIV antibody despite evidence of HIV infection. One child who had seronegative results from 6 months until 18 months of age seroconverted at 22 months of age, one child had HIV antigen in his serum, and one child synthesized IgM against HIV (see below).

Diagnosis by the acquisition of new bands on Western blot is demonstrated in Fig 2. Samples were collected at 2, 4, and 6 months of age from an infant who had met clinical criteria for AIDS by 4 months of age (patient 7). The acquisition of IgG antibody against p55, p51/66, and gp41 at 4 and 6 months of age confirms endogenous antibody synthesis and HIV infection in this child. Antibody against p17, p24, p31, and gp160 was persistently positive until this child's death at 7 months of age. Two of 20 children demonstrated new bands confirming HIV infection.

Four of the 20 children had evidence of anti-HIV IgM synthesis. Two children had IgM against HIV at birth; the other 2 children synthesized IgM

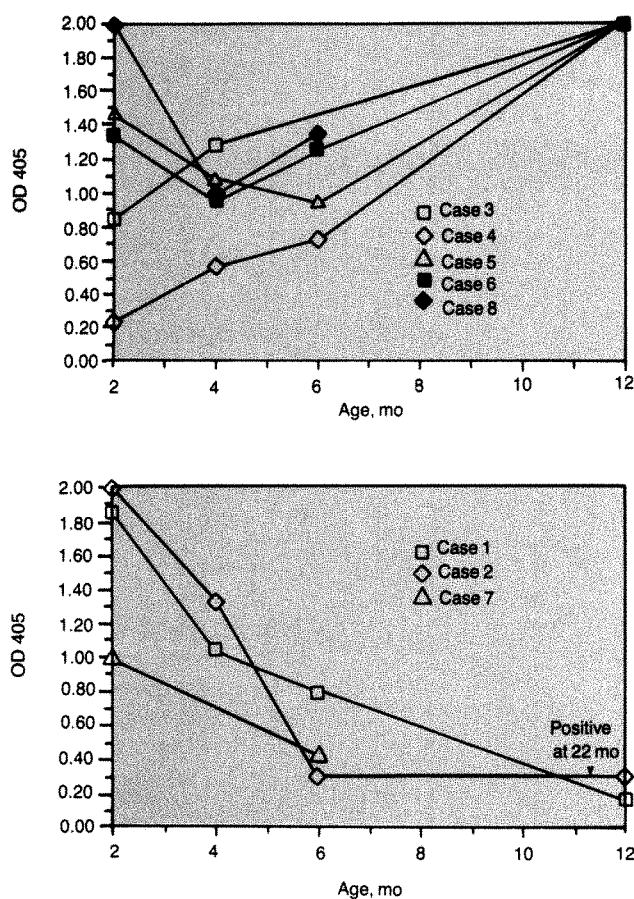


Fig 1.—Graph showing anti-human immunodeficiency virus antibody level. Serum collected at the indicated ages demonstrate increasing antibody levels (top) and decreasing antibody levels (bottom) in infants infected with human immunodeficiency virus. OD 405 indicates optical density at 405 nm.

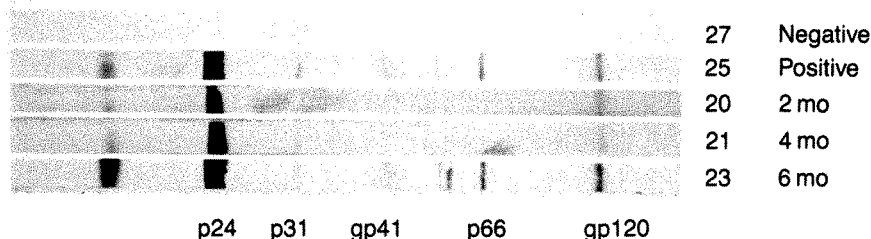


Fig 2.—Western blot profile showing anti-human immunodeficiency virus IgG antibody. Sequential samples of serum were assayed in a child who developed clinical criteria for acquired immunodeficiency syndrome by 4 months of age. Note acquisition of bands against p55, p66, and gp41.

against HIV by 4 months of age. Of the 4 children with IgM-seropositive results, 3 subsequently developed anti-HIV antibodies of the IgG class (1 at 22 months of age). The other child lost anti-

body positivity (IgG and IgM) by 1 year of age but has slow growth and a low T4:T8 ratio, ie, less than 1.

Assay by antigen enzyme-linked immunosorbent assay revealed that 5 of 20

children had antigenemia by 4 months of age. Four of these children have gone on to develop clinical criteria for P2D classification by 1 year of age.⁸

In summary, a total of 17 positive assays could be documented in 8 of the 20 children by 6 months of age. Increasing antibody titer against HIV and antigen detection were equally sensitive, ie, positive in 5 children by 1 year of age. The IgM testing confirmed infection in 4 children and was the first positive test in 3. The acquisition of new IgG bands confirmed infection in 2 children. These 8 children, presumed to be infected, were compared with the 12 other children who served as controls for an assessment of the onset of disease processes presented below.

Natural History

There were no significant physical differences between the HIV-infected and the noninfected infants at birth (Table 2). Twenty-five percent (5/20) of the infants had birth weights below 2500 g; 2 of these infants later proved to be HIV infected. Similarly, 5 children were born before 35 weeks of gestation, 2 children in the infected group and 3 children in the noninfected group. One child in each group was small for gestational age. No child had dysmorphic features at birth, although by 9 months of age, 1 infected infant had mild dysmorphism consisting of hypertelorism, frontal bossing, and a flattened nasal bridge.¹⁹ Drug withdrawal symptoms were observed in 1 of the infected and 9 of the noninfected children ($P = .02$).

The prevalence of clinical abnormalities in infected children was compared with abnormalities in noninfected children by age of onset (Fig 3). Adenopathy was the most common abnormality observed in the HIV-infected children. This occurred in a significantly higher percentage of infected children (87%) than noninfected children (8.5%) by 4 months of age ($P < .001$). Splenomegaly tended to occur in children with adenopathy but was not reported in a statistically significantly greater proportion of infected children (62.5%) than found in the control population (25%; $P = .17$).

Hepatomegaly was observed in 5 of the infected children, compared with 1 of 12 noninfected children ($P = .02$). This tended to occur late in the first year

Table 2.—Perinatal and Neonatal Characteristics of Infants at Risk for HIV*

Characteristics	No. of Infants		
	Infected (n = 8)	Noninfected (n = 12)	Total (%) (N = 20)
Birth weight, g			
<2500	2	3	5 (25)
2501-3500	5	8	13 (65)
>3500	1	1	2 (10)
Gestational age, wk			
<35	2	3	5 (25)
38-40	4	7	11 (55)
41-42	2	2	4 (20)
Small for gestational age	1	1	2 (10)

*HIV indicates human immunodeficiency virus.

usually noted on the face and trunk and responded to topical treatment with hydrocortisone.

The Denver Developmental Screening Test was failed by 62.5% of the infected children and 25% of the noninfected children ($P = .17$). The incidence of language delay was not different in the two populations, occurring in four of the infected children and in three controls ($P = .36$). There was, however, a significant difference in the neurologic examination findings. Four of the infected children (50%) who had failed motor milestone assessments had hypertonicity and hyperreflexia. No abnormal upper motor neuron signs were reported in control children ($P = .01$).

Infections and Illnesses

Table 3 shows the frequency of infections in these children. Four of the infected children had infections meeting the diagnostic criteria for AIDS: two developed histologically proved *Pneumocystis carinii* pneumonia by 6 months of age. One of these children also had presumptive central nervous system toxoplasmosis. Two other children had recurrent serious bacterial infections, including sepsis and septic arthritis in one and recurrent sepsis and pneumonia in another.

The most frequent type of bacterial infection that distinguished the immunodeficient children from the control children was pneumonia. Five of the HIV-infected children had at least one episode of lobar pneumonia requiring antibiotic therapy. This occurred in 1 of the 12 noninfected children ($P = .02$). Two HIV-infected children had documented bacterial sepsis ($P = .15$). There was also a significantly greater incidence of failure to thrive occurring in 4 of the 8 infected children and none of the controls ($P = .01$). Two infected children had radiologic evidence of lymphoid interstitial pneumonitis during the study period ($P = .15$).

There was not a significant difference in the incidence of documented upper respiratory tract infections in the infected children. There also was not a significant difference in episodes of gastroenteritis in these children. On the other hand, unusual enteric pathogens were identified only in the infected children, including cryptosporidium in a

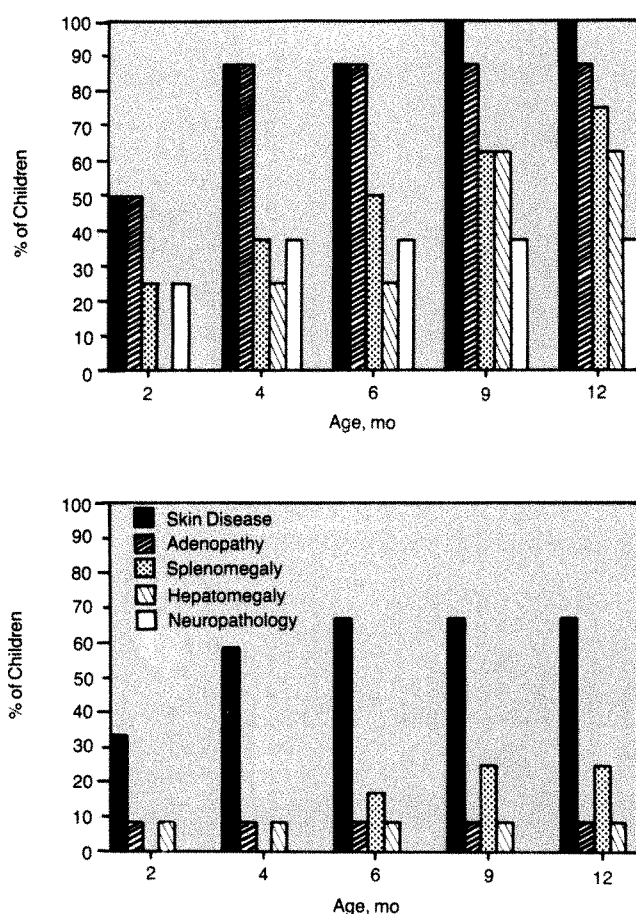


Fig 3.—Graph showing prevalence of clinical abnormalities. Percentage of children with the indicated clinical abnormality by age of development is shown for human immunodeficiency virus-infected (top) and noninfected (bottom) children.

of life. All of the infected children and two thirds of the noninfected children developed dermatitis. Candidial dermatitis accounted for the observed skin disease in half of the infected children and

in all of the noninfected children. The other skin abnormality, seen only in the infected children, was a generalized seborrheic rash that persisted in 3 children for several months. The rash was

Table 3. — Illnesses in Infants at Risk for HIV Infection in the First Years of Life*

	No. of Cases/Total No. of Patients		
	Infected	Controls	Significance†
AIDS defining infection‡	4/8	0/12	$P = .01$
Lobar pneumonia	5/8	1/12	$P = .02$
Failure to thrive	4/8	0/12	$P = .01$
Infectious dermatitis	6/8	4/12	$P = .17$
Persistent thrush	4/8	1/12	$P = .11$
Sinusitis	2/8	0/12	$P = .15$
Otitis media (≥ 2 episodes)	3/8	4/12	$z > .99$
Upper respiratory tract infection	21/8	19/12	$z = .15$
Gastroenteritis	24/8	16/12	$z = .76$
Deaths	2/8	0/12	$P = .15$

*HIV indicates human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.

† P values were determined using a Student t test and z values were determined using a z test.

‡There were two cases of *Pneumocystis carinii* pneumonia (one with presumed central nervous system toxoplasmosis) and two cases of recurrent bacterial infections.

child with *P. carinii* pneumonia, persistent adenovirus infection, and cytomegalovirus enteritis confirmed at autopsy.

Immunologic Studies

The most commonly observed laboratory abnormality in the children with HIV infection was hypergammaglobulinemia. This was observed in 50% of the infected children by 4 months of age and in 75% of the infected children by 9 months of age. None of the control children had hypergammaglobulinemia ($P < .001$). The next most frequent immunologic abnormality was an inverted T4:T8 ratio (< 1). This abnormality developed gradually and could be demonstrated in half of the infected children by 9 months of age. All but one infected child demonstrated an abnormal T4:T8 ratio by 18 months of age. Four children developed a frank deficit of T helper cells (< 800 cells/mm³). Lymphopenia was relatively uncommon in this population, occurring in only two of the most severely affected children late in the first year of life. No immunologic abnormalities were documented in the control children.

Classification

Six of the eight children developed HIV-mediated disease (Centers for Disease Control P2) by 6 months of age, as did a seventh child by 1 year of age. Four of these infected children developed AIDS and qualified for P2D class; the other three had milder signs and/or symptoms (P2A). One infected child re-

mained asymptomatic (P1A) during the study. She had been documented as HIV-infected by transient IgM seropositivity (2 and 4 months of age), which was unconfirmed until she developed IgG seropositivity at 22 months of age.

COMMENT

Conclusive diagnosis of congenital infection has always posed problems for pediatric practitioners. For many of the agents producing perinatal morbidity (ie, toxoplasmosis, cytomegalovirus, and rubella), recognizable clinical syndromes and diagnostic procedures have been established. Similar protocols are necessary to identify perinatal HIV transmission to infants.

We have been able to document infection in 8 of 20 infants at risk by 6 months of age using a battery of diagnostic techniques. This suggests a perinatal transmission rate of approximately 40% in this small population. This is similar to the rate observed in European studies of 34%²⁰ and 24%.²¹ One explanation for our somewhat higher transmission rate, other than the small population size, is that the European studies did not include either Western blot profile comparison or IgM testing in their assays for infection.

Serologic diagnosis of HIV infection is the standard in adults. Presence of anti-HIV IgG in an infant merely confirms the maternal infectious status. Longitudinal collection and batch assay by routine enzyme-linked immunosorbent assay for demonstration of increasing anti-HIV antibody titer identified

five (63%) of eight infected children by 1 year of life. A sixth child (patient 2) became seropositive at 22 months of age. Two infected infants have not demonstrated increasing anti-HIV IgG titer by enzyme-linked immunosorbent assay; one of these children was antigen-positive at birth and did demonstrate new band synthesis against HIV (patient 7). Therefore, seven (88%) of eight infected children in our study demonstrated an IgG response to HIV infection. The other infected, IgG seronegative, IgM seropositive child (patient 1) had physical findings and an inverted T4:T8 ratio consistent with HIV infection.

Two infants developed new antibody specificities against antigens of HIV not present at birth as demonstrated by Western blot.²² In one child, this approach permitted identification of endogenous IgG synthesis against HIV despite declining total anti-HIV antibody. Pyun et al²³ provided a conceptually similar approach by assessing the onset of IgG synthesis by analysis of antibody subclasses against HIV.

The disadvantage of procedures that assess the onset of IgG antibody synthesis against HIV is the time requirement for longitudinal study. Another disadvantage with extensive implications is that not all infected children will synthesize IgG against HIV in the first 18 months of life. Others have also demonstrated extended periods for seroconversion after perinatal infection, ie, up to 3 years.⁹⁻¹¹ It is clear that synthesis of IgG against HIV in infected infants may not occur and cannot be the sole basis for conclusive diagnosis.

Assay for IgM against HIV confirmed infection in four, ie, 50%, of the children. In a study of African children at risk for infection, IgM seropositivity was demonstrated in a similar proportion of infants at risk.²⁴ Two of the children who were IgM antibody-positive lost both IgM and IgG reactivity to HIV (patients 1 and 2). One child seroconverted at 22 months of age. The other child has subsequently exhibited negative results on in all assays (patient 1). It would appear, therefore, that although IgM detection will also not identify all infected infants, it may be the only serologic marker of infection in some children.

The antigen detection system identified 62.5% of the infected children. This is similar to viral detection in adults by this approach.²⁵ The children who had measurable serum antigen appear to have a poorer prognosis. Four of five antigen-positive children developed clinical criteria for P2D classification and AIDS by the ninth month of life. A similar relationship between antigenemia and disease development has been demonstrated in the adult population.²⁶

The performance of HIV culture in this population was not attempted. Such studies are currently under way, but the data in the adult population indicate that this will also have incomplete sensitivity for the detection of infection.²⁷ Furthermore, HIV culture methods are not sufficiently standardized to be of use in the general medical community.

Although estimates of specificity of these assays cannot be developed from this small population, it is clear that more sensitive and specific assays must be developed for confirmation of HIV infection in infants. Improved culture techniques or polymerase chain reaction techniques should enhance the currently available detection systems.^{28,29}

The lack of completely sensitive diagnostic criteria for HIV infection in the infant population has prompted the need for an awareness of the early clinical and laboratory signs suggestive of HIV infection. The manifestations of HIV infection in children have previously been well documented,¹²⁻¹⁷ but this prospective study yields some important comparisons.

The earliest and most common manifestation in HIV-infected children was the development of unusual lymphadenopathy. This was usually associated with hypergammaglobulinemia and frequently with splenomegaly. Skin diseases, and particularly candidal dermatitis, were common in both the infected and control children, although the infected children had more severe and persistent infections. A seborrheic rash was observed only in infected children and may be useful for identification. The cause of this rash is unclear but may relate to either an unidentifiable chronic infection or circulating immune complexes in these children.

Language delay in the at-risk, nonin-

fectured population is common and, therefore, not specific for HIV infection. On the other hand, signs of neurologic disease appear to be a specific finding, documented in half of the HIV-infected infants by 6 months of age. Several of the neurologically affected children had no evidence of associated immunodeficiency disease at the time, suggesting that infants with HIV infection are particularly susceptible to dementia.^{30,31}

Failure to thrive was seen only in the HIV-infected infants. A syndrome of failure to grow, failure to develop, dermatitis, and early death was seen in two of the eight infected children.

The most common laboratory abnormality was hypergammaglobulinemia. Hypogammaglobulinemia has been reported in a small proportion of children with AIDS, but was not observed in this population.⁵

The T-cell changes were relatively slow to evolve and tended to associate with, but appear later than, clinical immunodeficiency. We did not find other distinguishing hematologic abnormalities in these children although it has been reported that thrombocytopenia may be an initial presentation of HIV disease.³²

The unusual infections characteristic of AIDS readily indicate a child's HIV status. The development of opportunistic and/or recurrent bacterial infections before 1 year of age is well documented and underscores the marked susceptibility of the developing immune system to HIV. Somewhat surprising was the marked incidence of lower respiratory tract infections in the children with HIV infection during the first year of life. Presumed bacterial pneumonia was the most common infection in this population. Pneumonia is recognized as a frequent presentation of congenital immunodeficiency diseases and may be seen in children with either B-cell or T-cell abnormalities.

Only one infected child remained in the P1 category at 1 year of age. Infection in this child was documented by IgM seropositivity. Three of the four children who have not developed AIDS did synthesize anti-HIV IgM. It would appear from this limited population size that anti-HIV IgM may be associated with a better prognosis in HIV-infected children. Anti-HIV IgM detected post-

natally may indicate infection late pregnancy (or at delivery) and, therefore, may be associated with the appearance of signs and symptoms later in life. It is also possible that IgM may confer some protection to the child. Long-term follow-up will be necessary to determine the significance of these observations.

Most of the infected children had onset of HIV-mediated disease by months of age. Half of the infected children met the criteria for AIDS within the first year of life. Only one of eight children was asymptomatic by the end of the study. This supports the concept that infants may be particularly susceptible to the effects of HIV infection and raises concern over the large number of children born to women at risk for infection.

Also of concern is that four of the infected children had such mild symptoms (P1A or P2A) that they could go undiagnosed in a busy pediatric clinic. It is certain that there are many young children who have congenital HIV infection who have not developed marked degrees of immunodeficiency or neurologic disease. It is clear from these data that physical examination and readily available laboratory assessment will identify most HIV-infected children in the first year of life. Primary pediatric practitioners serving populations who may have risk factors must increase their awareness of possible perinatal HIV infection. Recognition and anticipation of the poor clinical outcome of HIV infection in children confirms the need to develop early, aggressive diagnosis and intervention to reduce the anticipated impact of perinatal HIV infection.

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The Medical Outcomes Study

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Providing Reliable Medical Information to the Public

G. D. Lundberg (*JAMA*. 1989;262:945)

Origins of Cerebral Palsy

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• Analyses were undertaken to determine the causes of cerebral palsy in a prospective study of 43 437 full-term children. Presumed causes were found for about 71% of the 34 quadriplegic and 40% of the 116 nonquadriplegic patients with cerebral palsy. Risk estimates based on predictive models, adjusted for multiple factors, suggest that 53% of the quadriplegic patients with cerebral palsy could be attributed to congenital disorders, 14% to birth asphyxia, and 8% to other identified disorders. Thirty-five percent of the nonquadriplegic patients with cerebral palsy could be attributed to congenital disorders and 6% to other disorders. In the victims of cerebral palsy, characteristic consequences of birth asphyxia were more often the result of nonasphyxial disorders. These included meconium in the amniotic fluid, low 10-minute Apgar scores, neonatal apnea spells, seizures, persisting neurologic abnormalities, and slow head growth after birth.

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This study was undertaken to try to identify and quantitate the major causes of cerebral palsy (CP). The analyses were based on specific disorders that might damage a child's brain. The most widely discussed of these disorders is birth asphyxia, with some people claiming that it is a frequent and others

For editorial comment see p 1139.

that it is a rare cause of CP. In recent years, the latter view has gained credence because very few victims of CP have had an asphyxial disorder recognized at birth.¹⁻¹⁰ This failure to recognize asphyxial disorders in victims of CP

could be misleading, because it is possible that such disorders are being missed or that insufficient cases have been analyzed to find a correlation between them and CP. The first goal of the present study was to determine how much of a role birth asphyxia has in the genesis of CP. A second goal was to quantitate the roles of chronic antenatal hypoxia disorders, congenital disorders, infections, trauma, hypoglycemia, oxytocin, and other prenatal and postnatal factors as causes of CP.

Most studies that have attempted to determine if birth asphyxia is a cause of CP have used low Apgar scores and fetal distress to identify asphyxia.^{1,10-19} Low Apgar scores and fetal distress are often nonhypoxic in origin, so their use as indicators of birth asphyxia could misattribute some nonasphyxial CP to asphyxia.^{2,20,21} We explored this possibility by seeing how many victims of CP who had low Apgar scores had a nonasphyxial disorder as the basis for their CP.

The final goal of the present study was to determine if some of the major causes of CP produce clinical findings that are distinctive enough to make their use a valid method for identifying the cause of CP in individual victims of CP. We particularly wanted to see if the neonatal manifestations of asphyxia-caused CP overlap the neonatal manifestations of CP caused by other disorders. For example, neonatal apneic spells, newborn neurologic abnormalities, and early neonatal seizures are well-known consequences of birth asphyxia.^{1,11,13,22} Is their presence proof that CP had an asphyxial origin or are they sometimes manifestations of CP caused by other disorders? We looked for an answer to this question.

METHODS

Data from the Collaborative Perinatal Study (CPS) of the National Institute of Neu-

rological and Communicative Disorders and Stroke, Bethesda, Md, were utilized in this investigation.²³⁻²⁷ The CPS was undertaken to identify fetal, intrapartum, and neonatal events that affect children's development. Its major aim was to determine if there are preventable causes of CP and other neurologic disorders. Cerebral palsy was defined as a chronic disability due to abnormal control of movements or posture that appears early in life and was nonprogressive. The CPS prospectively followed the course of the pregnancies of 58 947 women in 12 medical school-affiliated hospitals in different regions of the United States between 1959 and 1966. Events of gestation, labor, delivery, and the neonatal periods were recorded, as well as children's psychomotor, sensory, and physical development to 7 years of age. Detailed descriptions of the sampling methods, definitions, and study procedures have been published.^{16,23-29} The last neurologic examination in the study was conducted in 1973, at which time all the data became available for analysis on computer tapes in 1976. These data are still being analyzed today, because they comprise the largest and most complete set of prospectively collected information ever gathered to study the genesis of CP.

The current study focuses on two groups of full-term CPS children, 127 who had CP diagnosed by neurologic examination at 7 years of age and 23 who had CP diagnosed at 1 year of age and then died before reaching 7 years of age. The 150 children in these two groups include all CP cases, from mild to severe, in a subset of 43 437 full-term CPS children. *Full-term* was defined as birth at or after 37 weeks of gestation. Thirty-four of the 150 children had quadriplegic and 116 had nonquadriplegic CP. The children with quadriplegic CP were those who had abnormalities in the control of all four extremities. Children with hemiplegic, diplegic, and paraplegic CP were included in the nonquadriplegic category. Of the original 58 957 children in the CPS, 2865 could not be analyzed because their mothers delivered at a non-CPS hospital. Another 12 655 children were not included in the current analyses because they were born before term or lacked follow-up information. Most of those who lacked follow-up information had moved away from the CPS study center where they were born before the

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Table 1.—Disorders Included in Two Composite Categories*

Birth asphyxial factors (47 children were exposed to one or more of the following antenatal disorders and had seizures in the neonatal period)†
Abruptio placentae (n = 2)
Tight knot in umbilical cord (n = 1)
Active labor lasted >20 h (n = 10)
Tumultuous labor (n = 1)
Maternal shock (n = 4)
Severe fetal hemorrhage (n = 3)
Umbilical cord tight around neck or body (n = 11)
Umbilical cord prolapse (n = 4)
Arrested progress of active labor (n = 8)
Persistent high uterine tone during labor (n = 3)
Maternal anesthesia accident (n = 4)
Severe vaginal bleeding at delivery (n = 11)
Chronic antenatal hypoxic disorders (16 689 children were exposed to one or more of the following antenatal disorders)
Maternal anemia (third trimester hemoglobin level <90 g/L (n = 3059)
Midpregnancy maternal hemoglobin value \geq 125 g/L (low first trimester blood volume expansion) (n = 5740)
Disorders that produce low uteroplacental blood flow
Preeclampsia and chronic gestational hypertension (n = 2164)
Unexpected drop in third trimester maternal blood pressure (n = 3985)
Postterm delivery (n = 2968)
Multiple births (n = 537)

*There were 43 437 full-term children in the study as a whole. Brain damage due to any of the above disorders could have been the result of ischemia, as well as the consequence of asphyxia or hypoxia.

†Neonatal seizures also had to be present for a case to be included in the birth asphyxia category.

Table 2.—The Rate of Clinical Findings per 1000 Births With Birth Asphyxia and Congenital Disorder Subgroups

Clinical Findings	Rate/1000 Births (No. of Children)				Total No. of Children
	Birth Asphyxia		Congenital Disorders		
	Absent	Present	Absent	Present	
Meconium in amniotic fluid	198 (8624)	200 (6)	194 (7633)	241 (997)*	8630
Apgar scores at 1 and 10 min 0-3 and 0-5	6 (253)	383 (18)	5 (206)	16 (65)*	271
0-3 and 6-10	39 (1681)	213 (10)*	37 (1454)	57 (237)*	1691
Neonatal hypotonia	13 (554)	702 (33)*	10 (377)	51 (210)*	587
Neonatal seizures	3 (155)	...	2 (82)	18 (73)*	155
Neonatal apneic episodes	3 (118)	340 (16)*	2 (75)	14 (59)*	134
Neurologic abnormalities in neonatal period	95 (4121)	1000 (47)*	81 (3186)	238 (982)*	4167
Neurologic abnormalities develop during first year of life	57 (2450)	0	54 (2114)	81 (336)*	2450
Head circumference 1st to 10th percentiles at birth	59 (2539)	149 (7)*	57 (2233)	76 (313)*	2546
Head circumference increase <10 cm in first year of life	38 (1639)	455 (11)*	37 (1455)	47 (195)*	1650
Total No. of children in the category	43 390	47	39 313	4124	43 437

* $P < .005$ for rate between clinical finding present and absent within a subgroup.

reached 7 years of age. Preterm children, those born before 38 weeks of gestation, were not included in the current study, because the clinical management of preterm children has changed too much since the CPS data were collected to be sure that the CPS findings on such children are valid for children born before term today.

The following approach was used to try to determine if birth asphyxial disorders are commonly being missed in studies of the ori-

gins of CP. Birth asphyxia severe enough to damage the brain causes characteristic clinical findings in the neonate including low 10-minute Apgar scores, seizures, apnea spells, hypotonia, and other neurologic abnormalities (Tables 1 and 2).^{1,11-18} If analyses found that all cases of CP that follow one or more of these clinical findings were explained by specifically identified brain-damaging disorders, the possibility would be increased that the analyses were recognizing all of the cases

of asphyxia-initiated CP.

Another strategy was employed to try to insure that enough children were being analyzed to accurately assess the role of birth asphyxia in CP. Both CP and individual birth asphyxial disorders have low frequencies in the general population, so if birth asphyxia is responsible for only a few percent of CP cases, a larger study than has been undertaken to date might be needed to determine whether a correlation exists between individual asphyxial disorders and CP. To try to overcome this problem, we consolidated all of the disorders that can cause birth asphyxia in the current study into a single composite category, which we termed *birth asphyxial factors* (Tables 1 and 3). By this method, enough birth-asphyxiated children should be present to quantitatively assess the role of birth asphyxia in CP. To insure that children placed in the birth asphyxia category experienced enough asphyxia or hypoxia to affect their brains, they also had to have had one or more seizures in the neonatal period. The CP that follows birth asphyxia is usually the result of cerebral ischemia or vascular occlusions that lead to necrosis and cerebral edema, which in turn almost always produce seizures in the neonatal period.^{13,18,30-32} Using these criteria, 47 children who were alive at 1 week of age were classified as having experienced birth asphyxia (Tables 1 and 3).

The criteria to be placed in a composite category labeled *chronic antenatal hypoxia disorders* (Tables 1 and 3) were met by 16 689 children. Disorders and conditions that can cause antenatal hypoxia or ischemia for several days or longer were classified as chronic antenatal hypoxia disorders. Such hypoxia is most often the result of chronic low blood flow from the uterus to the placenta, maternal anemia, or a continuation of pregnancy beyond 42 weeks of gestation (postterm).^{24,33} The most frequent causes of low uteroplacental blood flow are subnormal maternal blood volume expansion during the first trimester of pregnancy, preeclampsia, unexpected third trimester drops in maternal blood pressure, and multiple fetuses.^{24,34-38} In a normal pregnancy, maternal blood volume expands by about 50% between the 8th and the 14th weeks of gestation.³⁵ More of this blood volume increase is due to plasma volume expansion than to erythrocyte increase, so hemodilution normally reduces hemoglobin levels and hematocrit values before midgestation. In the present study, mid-second trimester hemoglobin levels equal to or greater than 125 g/L were used as an indication that blood volume increase may have been subnormal. We would have used a higher hemoglobin level to identify gravidas with possible low blood volume expansion if the women in the CPS had routinely received supplemental iron during pregnancy. They did not rou-

Table 3.—Frequency Distribution of Cerebral Palsy Status by Composite and Individual Risk Factors

Variable	No. (%) of Children			Total
	Quadriplegic Cerebral Palsy	Nonquadriplegic Cerebral Palsy	No Cerebral Palsy	
Composite risk factor categories				
Birth asphyxia	6 (12.8)*	3 (5.4)	33 (80.9)	47
Chronic antenatal hypoxia	13 (0.1)	44 (0.3)	16632 (99.6)	16689
Major congenital malformations				
Central nervous system	7 (0.8)*	17 (2.0)*	843 (97.2)	867
Non-central nervous system	12 (0.4)*	17 (0.5)*	3181 (99.1)	3210
Congenital syndromes	2 (0.9)	6 (2.7)*	215 (94.6)	223
Minor congenital malformations	12 (0.2)*	43 (0.6)*	6423 (99.2)	6478
Birth trauma	1 (0.3)	1 (0.3)	374 (99.5)	376
Fetal/neonatal hypoglycemia	1 (0.5)	1 (0.5)	207 (99.0)	209
Symptomatic intoxications	1 (1.3)	1 (1.3)	74 (97.4)	76
Central nervous system infections	3 (1.6)	6 (3.2)*	175 (95.1)	185
Motor disorders, siblings	2 (0.4)	5 (1.0)*	504 (98.6)	511
Individual risk factors				
Maternal seizure disorder	2 (0.2)	8 (0.7)	1097 (99.1)	1107
Used gas anesthesia	12 (0.1)	42 (0.3)	13753 (99.6)	13812
Used oxytocin	5 (0.1)	15 (0.2)	6703 (99.7)	6723
Respiratory distress syndrome	2 (4.0)	0	43 (96.0)	50
Cigarette smoking	11 (0.1)	50 (0.4)*	13657 (99.6)	13718
All cases in study	34 (0.1)	116 (0.3)	43287 (99.4)	43437

*P<.01 compared with all cases in study.

tinely receive such iron. A gravida was identified as preeclamptic when she had two or more gestational diastolic blood pressures equal to or greater than 86 mm Hg accompanied by 1+ or greater proteinuria. An unexpected third trimester blood pressure drop was diagnosed when diastolic blood pressure decreased 20 mm Hg or more between third trimester clinic visits to a value of 60 mm Hg or less. A preliminary analysis found that such blood pressure drops were followed by a greater-than-expected frequency of long-term neurologic abnormalities.³⁸ Multiple births were placed in the chronic antenatal hypoxia category, because uteroplacental blood flow is usually low for individual fetuses when two or more fetuses are present.³⁷

The problem of limited sample size could have prevented previous studies from identifying some nonasphyxial causes of CP, so we put nonasphyxial disorders that have common mechanisms of action into single composite categories for the current analyses (Table 3). Examinations during the first year of life were the basis for diagnosing congenital malformations. One composite group contained children who had major central nervous system (CNS) malformations. Another composite group contained children who had major non-CNS malformations. A third composite category included children who had

minor congenital malformations. Major malformations were those that might shorten life span; and minor malformations, those that did not pose such a threat. A fourth category included children who had congenital syndromes. This congenital syndrome category contained children who had recognized combinations of phenotypic findings that have been given names and have a congenital origin. The composite category motor disorders in siblings contained children who had one or more siblings with a chronic motor disorder. The composite category, birth trauma, included children with skull fractures, children on whom high forceps had been used, and cases in which the progress of active labor had been arrested for greater than 10 hours.

Conditions that can cause severe fetal or neonatal hypoglycemia were combined into a composite category labeled *fetal/neonatal hypoglycemia*. It included children who had symptomatic hypoglycemia during the neonatal period and children whose diabetic mothers had one or more episodes of severe hypoglycemia during pregnancy.²⁷ Two composite categories of postneonatal disorders were also analyzed: symptomatic intoxications and CNS infections. Symptomatic intoxications were the result of accidental ingestions of drugs and chemicals. The most frequent of the drugs and chemicals were kerosene, gasoline, salicylates, and lead.

Central nervous system infections include encephalitis and meningitis that develop between birth and 1 year of age.

Other possible risk factors for CP were analyzed individually rather than in composite categories (Table 3). Among these risk factors, unexplained gestational proteinuria describes gravidas who had 2+ or greater proteinuria that was unexplained by hypertension or urinary tract infections. There were 643 gravidas in this category. Previous analyses of the CPS data found that such proteinuria was followed by a greater-than-expected frequency of long-term neurologic abnormalities.³⁸ Other maternal pregnancy factors that were analyzed individually for their relationship to CP were cigarette smoking, total maternal pregnancy weight gain, and diabetes mellitus.²⁴ Forty-eight percent of the women smoked during pregnancy and 1.6% had pregravid or gestational diabetes mellitus. Data on cigarette smoking were collected at each clinic visit throughout pregnancy and analyzed by the average number of cigarettes smoked per day.²³⁻²⁷ Addiction to illicit drugs was not included as a risk factor in the analyses, because no detailed information was collected on the drugs used, their amounts, or the timing of their use.

Delivery factors that were analyzed individually for their relationship to CP were the use of oxytocin to start or to potentiate labor, breech delivery, and the use of gas anesthesia (Table 3).^{24,27} Oxytocin was not included in the composite birth asphyxia category, because it was administered so frequently (67% CPS gravidas) that it could be individualized as a risk factor.

Neonatal factors that were individually analyzed were the sex of the child, the presence of the respiratory distress syndrome (in children), and hyperbilirubinemia (448 children). Hyperbilirubinemia was diagnosed when neonatal serum bilirubin level reached or exceeded 307 $\mu\text{mol/L}$.

The results of a nonverbal intelligence test (Science Research Associates test) given to each gravida was analyzed for its relationship to CP.²⁷ Noneclamptic maternal seizure disorders were also analyzed as a separate risk factor for CP. Such seizures had a somewhat higher frequency in the CPS women than in women in the general population (Table 3). Demographic factors that were analyzed individually included race (46% white, 46% black, 8% other), years of maternal education, family income, and the type of employment of the head of household.²⁷

Studies were also undertaken to see if clinical findings, particularly those in the neonatal period, could be used to help identify the causes of CP. We particularly wanted to know if birth asphyxia produced a pattern of clinical findings that was distinctive enough to distinguish asphyxia-initiated CP from CP

Table 4.—Rate per 1000 Births, Relative Risk, Attributable Risk, and 95% Confidence Intervals for Risk of Quadriplegic Cerebral Palsy (CP) by Risk Factors

Model No.	Risk Factors in Model	Rate/1000 Births by Specified Risk Factors*	Relative Risks (95% Confidence Intervals)	Attributable Risks (95% Confidence Intervals)
1	Composite of all risk factors	3 (21)	12.9 (5.6, 29.5)	0.71 (0.56, 0.86)
2	Birth asphyxia	120 (6)	52.5 (11.0, 250.4)	0.14 (0.03, 0.26)
	Congenital disorders	3 (17)	8.3 (4.1, 16.8)	0.53 (0.39, 0.68)
	Central nervous system infections	15 (3)	15.4 (4.6, 51.8)	0.08 (–0.01, 0.17)
3	Congenital disorders			
	Malformations			
	Central nervous system	8 (7)	8.2 (3.6, 20.9)	0.18 (0.06, 0.30)
	Non-central nervous system	4 (12)	5.0 (2.4, 10.6)	0.28 (0.15, 0.41)
	Minor malformations	2 (12)	1.9 (1.3, 2.6)	0.10 (0.07, 0.12)
	Congenital syndromes	8 (2)	5.2 (1.2, 22.6)	0.05 (–0.01, 0.10)
	Motor disorders, siblings	4 (2)	4.6 (1.1, 19.5)	0.06 (–0.02, 0.11)

*Number of victims of CP are in parentheses in this column.

Table 5.—Rate per 1000 Births, Relative Risk, Attributable Risk, and 95% Confidence Intervals for Risk of Nonquadriplegic Cerebral Palsy (CP) by Risk Factors

Model No.	Risk Factors in Model	Rate/1000 Births by Specified Risk Factors*	Relative Risks (95% Confidence Intervals)	Attributable Risks (95% Confidence Intervals)
1	Composite of all risk factors	7 (58)	3.9 (2.7, 5.6)	0.40 (0.34, 0.45)
2	Birth asphyxia	60 (3)	8.6 (1.1, 65.8)	0.01 (–0.01, 0.03)
	Congenital disorders	9 (45)	3.3 (2.3, 4.9)	0.35 (0.29, 0.41)
	Central nervous system infections	30 (6)	10.7 (4.6, 25.0)	0.05 (0.01, 0.08)
3	Congenital disorders			
	Malformations			
	Central nervous system	20 (17)	7.7 (4.5, 13.2)	0.13 (0.07, 0.18)
	Non-central nervous system	5 (17)	1.7 (1.0, 2.9)	0.06 (0.03, 0.09)
	Minor malformations	6 (43)	2.2 (1.4, 13.3)	0.18 (0.13, 0.27)
	Congenital syndromes	24 (6)	6.9 (2.9, 16.1)	0.04 (0.01, 0.08)
	Motor disorders, siblings	9 (5)	3.6 (1.4, 5.8)	0.03 (0.01, 0.06)
4	Maternal seizure disorder	7 (8)	2.9 (4.6, 25.0)	0.05 (0.01, 0.08)
	Cigarette smoking during pregnancy	4 (50)	1.5 (1.2, 1.9)	0.12 (0.10, 0.14)

*Number of victims of CP are in parentheses in this column.

of other origins (Table 2). The clinical findings analyzed were meconium in the amniotic fluid, low 1-minute and 10-minute Apgar scores, neonatal seizures, multiple episodes of neonatal apnea, small head circumference at birth (1st to 10th percentiles),³⁹ slow head circumference growth during the first year of life (<10 cm), and the child's age at which neurologic abnormalities first appeared (neonatal, in the first year of life, between 1 and 2 years of age).

Multiple logistic regression was the method used to identify risk factors that were significantly associated with CP.⁴⁰ Factors not significantly associated with CP in these analyses are not reported in the tables of this study, with the exception of disorders and factors that are sometimes claimed to be a cause of CP (Table 3). A method for estimat-

ing population attributable risk from these logistic regression models described by Bruzzi et al⁴¹ was utilized to estimate the relative contribution of each factor when adjusted for all of the other risk factors in the model. The recently developed methods of Benichou and Gail⁴² were employed to construct 95% confidence intervals for the relative risk and attributable risk estimates (Tables 4 through 6). For example, an attributable risk of 0.53 from model No. 2 in Table 4 indicates that 53% of the CP cases are estimated to be attributable to one or more congenital disorders, given adjustments for birth asphyxia and CNS infections. Up to four risk factors were included in each analysis for relative risk and attributable risk. Any risk factor with a pair-wise correlation coefficient of at least .04 with another risk

factor was incorporated into the same four-factor risk model, so that conditional risks could be estimated for each key factor.

RESULTS

There were 150 cases of CP in the present study (0.34%), a rate of 1 in 290 full-term children (Table 3). Only 9 (6%) of the 150 victims of CP had birth asphyxia as the presumed cause of their CP. Six of the 9 had quadriplegic and 3 had nonquadriplegic CP. There was no significant association of CP with chronic antenatal hypoxic disorders (Table 3). Based on attributable risk estimates, congenital disorders explained over half (53%) of the cases of quadriplegic CP in the study (Table 4). Fourteen percent of the cases of quadriplegic CP was attributable to birth asphyxia and 8% to CNS infections. Congenital disorders explained about one third and CNS infections about 1 of 20 of the cases of nonquadriplegic CP (Table 5). No cause could be identified for nearly 60% of the nonquadriplegic patients with CP. Birth asphyxia was not a significant antecedent of nonquadriplegic CP (Table 5).

Another perspective is gained by looking at the relative risks of the various risk factors for CP. Birth asphyxia had the highest relative risk for quadriplegic CP, 52.5 (Table 4). However, the low frequency of birth asphyxia in the population as a whole (47 of 43 437) gave birth asphyxia a much smaller role as a cause of quadriplegic CP (attributable risk, 0.14) than the 52.5 relative risk value might suggest. Central nervous system infections and a variety of congenital disorders had high relative risks for both quadriplegic and nonquadriplegic CP (Tables 4 and 5). The CNS malformations that were most often associated with CP were hydrocephalus (8 cases), meningomyelocele (5 cases), and encephalocele (3 cases). Cardiac malformations (18 cases) were the most frequent non-CNS malformations among the victims of CP. Neonatal seizures were 35% ($P<.01$) more frequent after oxytocin was administered than when it was not used, but there was no corresponding increase in the frequency of CP after oxytocin use (Table 3). Fetal/neonatal hypoglycemia and the use of gas anesthesia at delivery were not associated with greater-than-expected frequencies of CP (Table 3).

Low 10-minute Apgar scores, neona-

tal hypotonia, neonatal apneic spells, neonatal neurologic abnormalities, and slow head growth after birth are all well-known consequences of birth asphyxia that is severe enough to damage the CNS. In the present study, these clinical findings were more often associated with congenital disorders than with birth asphyxia (Tables 2 and 6). The same was true for neonatal seizures (Table 6). Apgar scores that were low at 1 minute and recovered to a normal or near-normal value by 10 minutes were present in only two children with CP who were in the birth asphyxia category, but they were present in six victims of CP whose CP had a congenital origin (Table 6).

Children exposed to birth asphyxial disorders had a very high frequency of intrapartum and neonatal deaths. One hundred sixty-nine (43%) of the 397 children who were stillborn, and 447 (47%) of the 952 children who died in the first week of life had been exposed to a specifically identified birth asphyxial disorder. Of the 47 children in the birth asphyxial category who were still alive at 1 week of age, 15 (32%) died during the first month of life and another 8 (17%) died before 7 years of age. Of the 24 who were alive at 7 years, 6 (25%) had quadriplegic CP; 3 (13%), non-quadruplegic CP; and 2 (8%), other chronic neurologic abnormalities.

COMMENT

Birth asphyxia accounted for 6% (9/150) of the CP cases in the study as a whole. This included 6 of 34 cases of quadriplegic and 3 of 116 cases of non-quadruplegic CP. No cases of CP due to birth asphyxia were likely missed in the analyses, because every child in the birth asphyxia category had neonatal neurologic abnormalities, and all 49 victims of CP in the study who had neonatal neurologic abnormalities had an explanation for their CP: 9 had birth asphyxia; 36, congenital disorders; and 4, CNS infections.

Congenital disorders explained nearly four times as many cases of quadriplegic CP than did birth asphyxia (attributable risks, 53% vs 14%, respectively). Congenital disorders were the only factor that explained a large number of the nonquadruplegic CP cases. It is also noteworthy that oxytocin, whose use

Table 6.—Risk Estimates for Cerebral Palsy (CP) When Selected Clinical Findings Were Present*

Variable	Rate/1000 Births With Specified Risk Factors Present	Relative Risks (95% Confidence Intervals)	Attributable Risks (95% Confidence Intervals)
Meconium not present in amniotic fluid			
Birth asphyxia	158 (3)	20.9 (8.2, 52.8)	0.03 (0.01, 0.06)
Congenital disorders	10 (34)	4.4 (3.2, 5.9)	0.26 (0.21, 0.31)
CNS infections	51 (8)	20.9 (8.2, 52.8)	0.03 (0.01, 0.06)
Meconium present in amniotic fluid			
Birth asphyxia	194 (6)	20.1 (7.8, 51.5)	0.12 (0.03, 0.22)
Congenital disorders	19 (19)	6.7 (3.7, 12.0)	0.43 (0.31, 0.55)
CNS infections	25 (1)	0	...
Apgar scores at 1 and 10 min			
0-3 and 0-5			
Birth asphyxia	316 (6)	8.0 (2.7, 24.0)	0.24 (0.06, 0.42)
Congenital disorders	129 (9)	4.1 (1.6, 10.4)	0.48 (0.31, 0.65)
CNS infections	0	0	...
0-3 and 6-10			
Birth asphyxia	182 (2)	12.5 (3.1, 50.2)	0.12 (-0.01, 0.25)
Congenital disorders	23 (6)	5.7 (2.4, 13.5)	0.47 (0.30, 0.64)
CNS infections	0	0	...
4-10 and 6-10			
Birth asphyxia	50 (1)	<1.0 (...)	...
Congenital disorders	9 (38)	4.3 (3.2, 5.8)	0.25 (0.20, 0.30)
CNS infections	48 (9)	11.2 (6.0, 21.0)	0.06 (0.03, 0.09)
Neonatal hypotonia absent			
Birth asphyxia	286 (4)	45.2 (17.6, 116.0)	0.03 (0.01, 0.06)
Congenital disorders	10 (40)	4.5 (3.4, 6.1)	0.26 (0.21, 0.31)
CNS infections	32 (6)	6.7 (2.2, 20.6)	0.04 (0.02, 0.07)
Neonatal hypotonia present			
Birth asphyxia	139 (5)	4.4 (1.8, 10.8)	0.14 (0.03, 0.24)
Congenital disorders	55 (13)	2.2 (1.2, 4.2)	0.32 (0.20, 0.43)
CNS infections	214 (3)	6.7 (2.2, 20.6)	0.09 (0.00, 0.17)
Neonatal seizures absent			
Birth asphyxia	...	0	...
Congenital disorders	10 (42)	4.4 (3.3, 5.9)	0.26 (0.21, 0.31)
CNS infections	43 (8)	12.7 (6.9, 23.3)	0.05 (0.02, 0.08)
Neonatal seizures present			
Birth asphyxia	180 (9)	2.4 (1.8, 5.5)	0.30 (0.11, 0.50)
Congenital disorders	134 (11)	3.2 (1.3, 8.4)	0.51 (0.32, 0.69)
CNS infections	77 (1)	0	...
Neonatal apneic episodes absent			
Birth asphyxia	234 (11)	27.4 (13.8, 58.6)	0.05 (0.02, 0.07)
Congenital disorders	15 (84)	4.6 (3.5, 6.1)	0.28 (0.23, 0.33)
CNS infections	56 (13)	9.1 (4.8, 17.1)	0.05 (0.02, 0.08)
Neonatal apneic episodes present			
Birth asphyxia	95 (3)	3.6 (0.9, 14.0)	0.08 (-0.04, 0.20)
Congenital disorders	51 (10)	3.7 (1.2, 11.1)	0.40 (0.22, 0.59)
CNS infections	100 (1)	3.2 (0.3, 29.2)	...
Head circumference 1st to 10th percentiles at birth			
Birth asphyxia	0	<1.0	...
Congenital disorders	38 (13)	5.4 (2.7, 10.9)	0.37 (0.22, 0.51)
CNS infections	117 (2)	4.1 (0.5, 32.9)	0.02 (-0.02, 0.06)
Head circumference 11th to 100th percentiles at birth			
Birth asphyxia	21 (9)	32.8 (17.4, 62.0)	0.06 (0.03, 0.09)
Congenital disorders	10 (40)	4.7 (3.5, 6.2)	0.28 (0.23, 0.34)
CNS infections	39 (7)	9.3 (4.9, 18.1)	0.05 (0.03, 0.08)

Table 6.—Risk Estimates for Cerebral Palsy (CP) When Selected Clinical Findings Were Present* (cont)

Variable	Rate/1000 Births With Specified Risk Factors Present	Relative Risks (95% Confidence Intervals)	Attributable Risks (95% Confidence Intervals)
Head circumference increase during first year of life, 0 to 9 cm			
Birth asphyxia	455 (5)	29.1 (7.9, 106.9)	0.13 (0.01, 0.25)
Congenital disorders	674 (13)	4.3 (2.0, 9.2)	0.31 (0.18, 0.45)
CNS infections	40 (2)	11.2 (2.1, 58.7)	0.05 (-0.02, 0.13)
Head circumference increase >9 cm during first year of life			
Birth asphyxia	103 (4)	14.0 (6.3, 30.9)	0.04 (0.01, 0.06)
Congenital disorders	9 (40)	4.7 (3.6, 6.3)	0.28 (0.24, 0.32)
CNS infections	37 (7)	8.8 (4.6, 16.9)	0.05 (0.02, 0.08)
Neurologic abnormalities first appeared in neonatal period			
Birth asphyxia	184 (9)	9.5 (5.1, 18.2)	0.12 (0.06, 0.18)
Congenital disorders	33 (36)	4.3 (2.9, 6.5)	0.47 (0.40, 0.55)
CNS infections	129 (4)	7.8 (3.2, 18.6)	0.05 (0.01, 0.09)
Neurologic abnormalities appeared between neonatal period and 1 year of age			
Birth asphyxia	0	<1.0	...
Congenital disorders	35 (13)	2.4 (1.5, 3.9)	0.17 (0.10, 0.24)
CNS infections	125 (4)	7.7 (3.1, 19.0)	0.07 (0.01, 0.12)
Neurologic abnormalities first appeared after 1 year of age			
Birth asphyxia	0	<1.0	...
Congenital disorders	2 (6)	2.1 (1.1, 4.2)	0.06 (0.04, 0.09)
CNS infections	8 (1)	0	...

*Minor congenital malformations were not included in these analyses. Number of victims of CP are in parentheses in second column. CNS indicates central nervous system.

was followed by an increased frequency of neonatal seizures, was not followed by a corresponding increase in the frequency of CP. Gas anesthesia, maternal seizures, maternal diabetes mellitus, and fetal/neonatal hypoglycemia were also not associated with a greater-than-expected frequency of CP.

Many previous studies have based their identification of asphyxia-originated CP on the presence of fetal distress and low Apgar scores.^{1,10-19} In the present study, low 10-minute Apgar scores were more often associated with congenital disorders than with birth asphyxia in victims of CP. Other clinical findings that characteristically follow birth asphyxia were also more often related to congenital disorders than to birth asphyxia in the children with CP. These findings include meconium in the amniotic fluid, neonatal seizures, neonatal apnea spells, neurologic abnormalities in the neonatal period, and slow head growth after birth. Therefore, these clinical findings, by themselves, cannot be trusted to distinguish CP of asphyxial origin from CP due to other causes. To establish that a child's CP was caused by birth asphyxia, a specific

asphyxial disorder needs to have been identified, gas and pH evidences of asphyxia must have been present in fetal blood, neurologic abnormalities should have persisted throughout the newborn period, and there should be no evidence of a nonasphyxial disorder that could have caused the CP. By itself, the finding of acidosis in fetal blood is not proof that birth asphyxia caused CP. Almost no correlation has been found between such acidosis and the presence of neurologic abnormalities in the neonatal period.⁴³⁻⁴⁵ The duration of bearing down during labor has a strong positive correlation with fetal acidosis, and it may be that the duration of bearing down is usually too short to produce even transient asphyxial brain damage.³⁶

No cause could be identified for 60% of the nonquadriplegic CP cases in the study. Birth asphyxia was not a significant risk for nonquadriplegic CP in the attributable risk analysis, and as previously mentioned, birth asphyxial disorders were not likely missed in the children with CP. Twenty-eight percent of the children who eventually developed nonquadriplegic CP had their neurologic abnormalities first recognized be-

tween 1 and 2 years of age. This long delay in the first appearance of neurologic abnormalities presumably reflects brain injury or maldevelopment that was less severe than that present in the children who developed quadriplegic CP. Seventeen of the 116 children with nonquadriplegic CP had recognized CNS malformations. This could be an underestimate of such malformations in the nonquadriplegic victims of CP, because the diagnostic tools available in the CPS missed many CNS malformations that could be identified by diagnostic tools that are in use today.

All the evidence that birth asphyxia caused only 6% of the CP cases in the current study might seem inconsistent with the frequent findings at autopsy of acute asphyxial lesions in the brains of children who were stillborn or who died in the newborn period as the result of birth asphyxial disorders. There is a simple explanation for the high frequency of these asphyxial lesions. Birth asphyxia or hypoxia that is severe enough to damage the fetal brain usually kills before or soon after birth.^{1,17,48} This is what apparently happened in the present study. Almost half of the 1349 children who were stillborn or died in the neonatal period died as the direct or indirect result of birth asphyxial disorders. Only 24 of the children in the birth asphyxial category survived to 7 years of age, and 11 of the 24 had CP or other neurologic abnormalities. The margin between the level at which intrapartum hypoxia begins to damage the fetal brain and the level at which it kills is very narrow.^{1,47} The ability of Myers and his associates⁴⁹⁻⁵² to produce severe brain damage in monkeys by inducing perinatal asphyxia might seem inconsistent with this view, but in fact their findings support it, because many of their monkeys died and almost all of the survivors had no neurologic abnormalities. A 1984 Oxford study produced still more evidence that CP is rarely the result of birth asphyxia. A failure of medical personnel to react to evidence of intrapartum hypoxia and asphyxia was followed by a greater-than-expected frequency of neonatal apnea and seizures, but not of CP.²²

Have obstetrical and neonatal clinical advances since 1966 when the last CPS child was born made the findings of the

current study obsolete? Probably not, because the advances that have reduced fetal and neonatal mortality in the intervening years have not produced a corresponding decrease in the frequency of CP.^{31,33-39} All the children with CP in the present study were born full-term, and it is unlikely that current obstetrical and pediatric managements could have prevented their CP, because most of the disorders that damaged their brains took place long before labor and delivery and were unrecognized at the time the damage occurred. Electronic fetal monitoring has come into widespread use since the CPS, and many hope that it is preventing some cases of CP by warning of asphyxia or hypoxia before irreversible brain damage takes place.

There is no convincing evidence that this hope is being realized.²¹ In a large, well-controlled study, MacDonald et al³⁸ used electronic fetal monitoring both to identify intrapartum asphyxia or hypoxia and to intervene to protect fetuses from further risk. These interventions reduced the frequency of neonatal seizures, but did not affect the frequency of subsequent neurologic abnormalities. These findings have their counterpart in the present study, where neonatal seizures were 35% more frequent when oxytocin was administered without a corresponding increase in the frequency of CP.

Finally, the findings of the present study underscore the importance of making accurate measurements and

observations on neonates to avoid misattributing nonasphyxial CP to birth asphyxia. Carefully recorded observations of a neonate's kidney, heart, and lung function can help to determine whether birth asphyxia caused CP, because birth asphyxia that is severe enough to damage the brain usually damages the kidneys, the lungs, and often the heart.^{2,19,47,61,62} The results of ultrasound examinations, computerized radiographic tomography, and magnetic resonance imaging studies can also be of value in distinguishing between CP of asphyxial and nonasphyxial origin.

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Book Review

Hypnosis and Hypnotherapy With Children, by Karen Olness and G. Gail Gardner, 431 pp, \$39, New York, NY, Grune & Stratton, 1988.

Hypnotherapy in the care of children has recently enjoyed a renaissance of interest and attention. Anecdotal reports of pediatric applications have been intriguing, yet hypnosis as a therapeutic modality in pediatrics has, with notable exceptions, remained out of the mainstream of medical understanding and use. Karen Olness, a pediatrician, and the late Gail Gardner, a psychologist, have, in this book, challenged clinicians to reexamine the potential contribution of hypnotherapy toward the primary care of a broad spectrum of pediatric conditions.

In a field so relatively new and untried, the authors have provided a general guide to the field, including introductory information, clinical applications, and research progress to date. The first chapters are devoted to the history of hypnotherapy and children, as well as to a review of the fundamentals of hypnosis and hypnotic responsiveness in children. There is a detailed chapter on hypnotic induction techniques. The body of the book covers applications for psychological and habit disorders, learning problems, pain control, and medical and surgical problems.

For the pediatric clinician, therapeutic applications are described for a variety of disparate conditions, including enuresis, encopresis, tic disorders, asthma, hemophilia, juvenile rheumatoid arthritis, headaches, cyclic vomiting, preparation for medical and surgical procedures, and coping with chronic or terminal illnesses. There are, as well, excellent discussions that help the clinician place this modality in context (eg, indications, limitations, and contraindications for use and the optimal involvement of parents). For the researcher, this book will continue to be a basic source. Each chapter is richly referenced. Studies cited range from case reports to well-designed experimental protocols.

For Olness and Gardner, hypnosis is defined broadly as "an altered state of consciousness" with focused attention and characteristic changes in cognition and receptivity. Hypnotherapy is seen as a treatment modality utilizing hypnosis but also relying on the skilled interventions of the clinician. The underlying mechanisms are acknowledged as not understood. A repeated theme throughout is that hyp-

nototherapy recruits and channels tendencies or "urges" present in every child, ie, to seek experience, mastery, social interaction, inner imagination, and wellness. Throughout the book the reader is admonished to view the hypnotic state as a talent that belongs to the child. The hypnotherapist is likened to a coach who helps develop this talent.

For the interested nonhypnotherapist pediatrician, two provisos apply. First, as a behavioral pediatrician not primarily trained in hypnotherapy (but the recipient of a 3-day workshop organized in part by one of the authors) I am impressed that the acquisition of hypnotherapy as a clinical tool requires live supervision. Too much of the technique relies on communication and interpersonal understanding to be learned solely from a text. The authors stress this point well.

Second, a dilemma arises with regard to the broader prerequisites for doing this sort of work. Olness and Gardner emphasize that a "hypnotherapist first must be a competent therapist." Their clinical descriptions and individualized therapeutic protocols belie their own in-depth understanding of child development and psychodynamic issues. At the same time, the care they describe is, for the most part, within the context and bounds of pediatric practice. The question, then, is whether current standard training in pediatrics provides the fundamental knowledge and skills necessary to acquire expertise in hypnotherapy. The authors do not address this directly, and readers will need to make their own assessment.

In sum, *Hypnosis and Hypnotherapy With Children* remains a pioneering effort by a pair of gifted and committed clinician-researchers. It persuasively presents the case that all children possess inner resources that may be tapped in the service of optimizing health and mastery. It is further evidence of the indivisibility of the links between mind and body, imagination and physiologic response, and play and well-being.

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The Pregnant Adolescent Prostitute

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• The issue of teenage pregnancy is one of paramount concern and has been covered extensively in the professional literature. Teenage prostitution, as well, has drawn attention from medical and social science researchers. An increasing number of teenage prostitutes are becoming pregnant and delivering infants. These young women constitute a high-risk group that merits professional investigation and requires sensitive clinical approaches. We describe the pregnancy and early postpartum outcomes of 61 teenage prostitutes (age range, 13 to 18 years) in Seattle, Wash, during the period from January 1987 to February 1988. The subjects' environment, prenatal care, drug use, contraceptive practices, repeated pregnancies, and risk for sexually transmitted diseases (including acquired immunodeficiency syndrome) are discussed. Two case examples are used for illustration.

(AJDC. 1989;143:1162-1165)

Teenage prostitution is a subject that has received relatively little attention in the professional medical literature. Even less attention has been given to the fact that many young women become pregnant in the course of their prostitution activities. It is estimated that at least 50% of all juvenile prostitutes have been pregnant at least once.¹ Adolescent pregnancy and child bearing, on the other hand, are subjects on which much has been written.¹⁻⁴ Specifically, there are studies on the effects of sexual abuse on young women,⁵ prevention,⁶ education,⁷ long-term outcome for adolescent mothers,^{8,9} and contraceptive behavior¹⁰ that emphasize the seriousness of the problem in contemporary society.

Existing literature on teenage prosti-

tution has focused on runaways and street life,¹¹ victimization,¹² legal considerations,^{13(p189-227)} and attempts at rehabilitation.¹³ In 1980, Weisberg¹ acknowledged that many adolescent prostitutes become pregnant. However, there is almost no reported data available on pregnant teenage prostitutes or pregnancy outcome.

The problems of teenage prostitution, when coupled with the risk of pregnancy and motherhood, are further exacerbated by the violent life-style of the streets and now by the risk of acquired immunodeficiency syndrome. Furthermore, those professionals who work with children and adolescents must be made aware of the victimization of these young people, not only by their families, pimps, and clients, but by a society to whom they are almost totally invisible, and by whom, if recognized, they are held responsible for their life situation. Abuse during childhood is a common factor in the lives of young people on the street. The negative sexual experience of early abuse often leads to a self concept of being sexually "devalued" and "spoiled," a "bad girl" who turns to a delinquent subculture for social acceptance, status, and income.^{12(pp812-855)}

Given the identified risks for child bearing at a young maternal age (ie, poor nutrition, substance abuse, and lack of prenatal care), it is difficult to find a risk group to which these young women do not belong.

It is estimated that there are 1 million runaways each year in the United States.^{12(p19)} The estimated number of adolescent prostitutes in the United States is 900 000; roughly two thirds or 600 000 of these prostitutes are female.^{12(p15)} A rough estimate of the number of young women in Seattle, Wash, under 18 years of age who are engaged in prostitution is thought to be between 400 and 500. This number is probably no greater than that which would be found

in any other city of comparable size.

Health and social services, if sought at all, are obtained by this population only for acute or crisis problems in busy emergency departments. Often these patients are not identified as prostitutes because complete medical histories are not taken or the appearance of the young woman does not fit the health professional's image of a prostitute. Furthermore, there is a reluctance among health professionals to confront the reality of teenage prostitution. These young women, when they have contact with health care providers, have been able to pass through the system almost unnoticed.

The adolescent medicine program at the University of Washington, Seattle, has provided medical care to street youth for the past 15 years through a network of free night clinics located throughout the downtown area of the city.

We have frequently encountered young women engaged in prostitution who present at clinics expressly for the purpose of determining pregnancy status. A large proportion are found to be pregnant. The study results reported herein describe our experience with 61 of these young women during the course of their pregnancies and during the early postpartum period.

The purpose of the project was to gather descriptive information on a sample of 61 young women and to facilitate access to appropriate health and social services. Two case examples are presented with a descriptive summary of the characteristics of the young women and their pregnancies.

CASE STUDIES

CASE 1.—Jean was a 17-year-old black teenager who was born in the Seattle area. She was relinquished by her natural mother, who was a drug addict and a prostitute. Jean's natural father was a drug addict.

Jean was adopted at 3 years of age by a

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white family. During her 10 years with this adoptive family, she was both sexually and physically abused. The sexual abuse began at 5 years of age by her adoptive father. By 11 years of age, she began running away from home regularly. She was then placed in numerous foster care homes from which she ran away. Jean dropped out of formal education at the age of 14 years, met her current pimp/drug dealer/boyfriend, and began prostituting. She was taken from Seattle to the San Francisco Bay area for a number of months to "work." She returned to Seattle, where she had a series of pimps/boyfriends. Recently, she became reinvolved with her original pimp.

Jean began experimenting with alcohol and drugs at 12 years of age and has been a regular cocaine and intravenous drug user for the past 4 years. She has been pregnant four times. Three of these pregnancies ended in abortion. The other pregnancy was carried to term.

During the pregnancy, Jean continued to use drugs and alcohol supplied by her pimp. She also continued to prostitute until late in her third trimester. She received no prenatal care. She presented in the emergency department of the hospital in labor.

Jean was allowed to take the infant from the hospital with no child protective service report being filed and no referral to a public health nurse.

Her relationship with her pimp has been very violent. This violence, as well as her drug addiction, has been used to control and intimidate Jean. She has been severely beaten by her pimp and he recently broke her jaw, which led to her hospitalization. She miscarried at that time. Jean considered filing charges, but was afraid for her child because child protective services had given temporary custody to the pimp's mother.

At this point, the young woman has lost custody of her child and is considering relinquishing parental rights. She has no stable living conditions and is continuing to prostitute and use intravenous drugs. Recently, she became reinvolved with her original pimp.

CASE 2.—Mary was a 16-year-old white teenager at the time of this study. She was born in the Seattle area to a mother who was a drug addict and alcohol abuser. Mary's natural mother lives in the Seattle area but is not allowed any contact with her children. Mary's natural father is unknown. Two sisters, aged 17 and 18 years, live in the Seattle area; both are involved in prostitution. One sister is pregnant, the other just delivered.

Mary's early home life was very chaotic. She and her sisters were separated at an early age due to sexual abuse in the home by her mother's customers. The girls were placed in foster care with relatives. Mary left

foster care at age 11 years and began prostituting for drugs and a place to sleep. Mary has a history of violent behavior and suicide attempts.

Mary has had numerous pimps and has traveled extensively up and down the West Coast. She has had the same pimp for the past 2 years. Mary became pregnant for the first time at age 14 years and received no prenatal care during her pregnancy. The child was removed from her custody and placed in long-term foster care. She became pregnant a second time at age 15 years. Again, she received no prenatal care and delivered in the back seat of a taxi bringing her to the hospital. She prostituted heavily for the first 8 months of the pregnancy and free-based cocaine up to the time of delivery. Child protective services intervened while the infant was still in the hospital.

The child was placed with Mary's eldest sister, who was pregnant at the time. Mary attempted to regain custody of her child but was mandated to complete drug treatment to accomplish this. She failed to complete drug treatment and has not followed up on her efforts to regain custody. The child is now in state foster care. Since losing custody of her child, Mary has been moving from place to place with her pimp.

SUBJECTS AND METHODS

To carry out the study, the Washington State Health Department, Bureau of Parent and Child Health, provided funding for a part-time social worker for case findings, follow-up, and data collection, as well as a part-time public health nurse to provide health and outreach services to these pregnant adolescents. These data were collected in Seattle from 1987 through 1988. The study data presented here focus primarily on the background and status of the young women.

The 61 subjects in this study were young women engaged in prostitution, 13 through 18 years of age, who were either pregnant or had recently delivered. Age and racial distribution are summarized in Table 1. New cases were identified by the project social worker in a variety of ways. Thirty-one of the 61 subjects interviewed between January 1987 and February 1988 were identified at the medical clinic in the King County Juvenile Detention Center, Seattle. Many young women are arrested for prostitution-related activities and are found to be pregnant at the time of their admission for health screening. The remaining 30 subjects were referred by a number of health and social service agencies serving street youth in the Seattle area. Due to the large number of referral sources, we believe that the young women in this study are an accurate representation of pregnant adolescent prostitutes in the Seattle area.

The social worker administered an open-

Table 1.—Age and Race of Subjects

Variable	No. (%) of Subjects (n=61)
Age, y	
13	2 (3.3)
14	3 (4.9)
15	14 (23.0)
16	27 (44.3)
17	13 (21.3)
18	2 (3.3)
Race	
Asian	1 (1.6)
East Indian	1 (1.6)
Native American	6 (9.8)
Black	24 (39.3)
White	27 (44.3)
Mixed	2 (3.3)

ended questionnaire to the project participants, which had been piloted in a university teen clinic with young teens who were pregnant. The questionnaires included discussion of family background and social history, sexual/physical abuse information, pregnancy status, health care status, drug use, child-bearing history, education history, living arrangements, contraceptive practices, and child protective services involvement. Examples of questions included, "Have you used drugs or alcohol during this or previous pregnancies?" "Have you used drugs or alcohol since delivery?" "Have you ever tried any form of birth control?" "If you are pregnant, what options for the pregnancy have you considered?"

The public health nurse, who joined the project in October 1987, initially contacted the young women for a pediatric and obstetric health needs assessment. Referrals were then made for prenatal or postnatal care, the Women, Infants and Children nutrition program, drug treatment, and other community services. The nurse also continued to follow up subjects, provide education and counseling, and monitor services. The public health nurse and the social worker met regularly for data collection and review, exchange of information, and joint planning of follow-up services.

RESULTS

A number of shared experiences or characteristics were common to the majority of subjects. None of the young women in the study sample came from an intact family. Child protective services had been involved with the majority of them as younger children. Many of the young women had been removed from their natural homes and placed in foster care.

Although fewer than half of the young

Table 2.—Contraceptive Use and Initiation of Prenatal Care

	No. (%) of Subjects
Contraceptive Use (n=61)	
Intermittent use	28 (45.9)
Never use	33 (54.1)
Prenatal Care (n=34)	
Month initiated	
3rd	2 (5.9)
4th	6 (17.6)
5th	10 (29.4)
6th	11 (32.4)
7th	4 (11.8)
8th	1 (2.9)

women admitted to having been physically or sexually abused as children, 37 refused to provide any detailed information to the interviewers about this sensitive subject. Fifteen (25%) of the subjects had mothers who were or are currently involved in prostitution. In some cases, the subjects' mothers had introduced them to prostitution.

Sixty-seven percent (n=41) of the sample had a family history of alcohol and other drug abuse. Several subjects described having been given alcohol and other drugs as children and being sexually abused by their mother's partners in the context of parental alcohol and other drug abuse. Sixty-five percent (n=40) of the young women in this sample had a known history of serious alcohol and other drug abuse. The entire spectrum of drug use has been reported by young women involved in the prostitution/street life-style. Other researchers have described a drug use rate among this population of 66% (n=10), which is consistent with that reported by our sample.¹⁶⁽¹⁷⁾

A lack of adequate education was common. Ninety percent (n=55) of the young women in the study were not in school at the time these data were collected. Of the 10% (n=6) who were in school, 3 were in alternative school programs and 3 were in general equivalency diploma programs. Due to the lack of sufficient education, emotional support, job skills, and social skills and the chaotic life-style, a hopelessness often pervades these young women's lives. Forty-one percent (n=25) of the subjects reported seriously considering or having attempted suicide within the past 12

months. Pregnancy appears to make them more vulnerable to depression and to manipulation by pimps and others on the street.

These young women came from varied socioeconomic and cultural backgrounds. Whites and blacks accounted for the largest percentage of subjects (Table 1). Living conditions for this group of young women varied widely. Some had somewhat stable living conditions. Others moved frequently, if not daily. Living situations at the time of the study are summarized below:

Living Situation	No. (%) of Subjects
Pimp/boyfriend/ husband	19 (31.1)
Mother/other relative	18 (29.5)
Social services/ detention	9 (14.8)
Female friends	6 (9.8)
Street	2 (3.3)
Not known	7 (11.5)

The young women in the study acknowledged that most of their pregnancies were unplanned. Moreover, they stated that they did not want to become pregnant again. Despite this, when asked if they were currently using contraceptives, most admitted that they were not using them or used them only sporadically (Table 2). Condoms were not used consistently, in part due to their unavailability at the time, the cost, or their customers' willingness to pay more if they would forego condom use.

Seventy-nine percent (n=48) of the young women reported having no involvement with the father of their child, and some were not sure of the father's identity. Thus, they expect and receive no financial or emotional support from him. The general lack of health care and specifically the lack of prenatal care is another common problem for these young women. On average, subjects in this study who received any prenatal care initiated that care at the end of the second trimester and made two prenatal appointments. At the conclusion of the study period, 38 (67%) of the 55 infants born to the study participants had been referred to child protective services. Most referrals were made prenatally or at the time of delivery by medical or mental health personnel. Forty (66%) of the 61 young women in the study had current involvement with

child protective services. The number of births to the young women who delivered is summarized below:

No. of Children (n=42)	No. (%) of Subjects
1	32 (76.2)
2	8 (19.0)
3	1 (2.4)
4	1 (2.4)

At the time of the study, 18 (29.5%) of the young women were pregnant, 41 (68.9%) had delivered, and 1 had died. A total of 55 infants were delivered and 4 infants (7.8%) died.

COMMENT

The teenage prostitutes in this study had many problems, as demonstrated by the results of this study, and illustrated by the case examples. The adolescents presented were typical in that once pregnant, a few would request an abortion, but the majority continued with the pregnancy. Relinquishment was almost totally rejected by the group; many, in fact, were glad to be pregnant, and felt that this would make their lives better. Despite wishing to keep their infants, most of the young women had no child care skills or any realistic idea of where they would live or how they would support their child. As a result, they received late or no prenatal care, lived in unhealthy environments and were erratic contraceptive users.

Teenage prostitutes present a challenge to social service and medical personnel alike. Their lack of trust of adults and authority figures often interfere with the establishment of a helping relationship. The teenagers' suspicion of adult motives, their transient and often violent life-style, their dependence on drugs, and their need to drop out of sight, often due to life-threatening circumstances, further their isolation and mistrust. Access to these teenagers by helping professionals is often barred by the controlling adult figure in their life. This person may be a pimp, an abusive boyfriend, or a relative, as was the case with the majority of our subjects.

When the element of prostitution is added to teenage pregnancy, a number of new factors must be considered in offering services. Some of the important areas to be addressed are sexual abuse, drug dependence, malnutrition, violence of a street-based life-style, sex

ually transmitted disease, (including acquired immunodeficiency syndrome), and the stress of the life-style combined with a lack of coping and social skills. Danger to the unborn or recently delivered child is ever present.

There was an 8% perinatal mortality rate among infants born to our study population. These infants face being born addicted to drugs, testing positive for human immunodeficiency virus (HIV), with birth defects or other congenital anomalies and prematurity and low birth weight. Infants living with their teenage mothers often face neglect and abuse at the hands of their parent or their mother's pimp or boyfriend. Despite the fact that many of the infants in our sample were removed from their mother's custody, they were frequently placed with the girl's mother, in whose home the girl may still be living while prostituting. When the child is not removed from the mother's custody, we have found that having an infant does not promote stability in her life. These young women usually continue with prostitution, drug involvement, and a destructive life-style. Many return to the streets within days of delivery.

Research indicates that young delinquent prostitutes exhibit considerable ignorance about sexuality, contraception, and sexually transmitted diseases (ID Tanabe and JA Farrow, unpublished data, 1989). Pregnancy seems to have little reality for them. Whether they are traumatized by their early experiences, involved with alcohol and

other drugs, or just developmentally immature, those seen in our clinics often do not come to terms with their pregnancy until the time of delivery. This disassociation with their condition appears to relate to the fact that they are often forced to continue in prostitution throughout their entire pregnancy. Furthermore, they are often totally unprepared to cope with the added responsibilities that a pregnancy imposes.

This population and their unborn infants are at an extremely high risk for HIV infection. Rosenberg and Weiner¹⁴ believe that adult prostitutes are not at high risk for acquired immunodeficiency syndrome due to their sexual activities. The young women in our study would appear to be at high risk. The prevalence of intravenous drug use among them and their partners as well as the large number of sexual partners (as many as 120 per month) make them vulnerable to HIV infection. Testing for HIV is not being requested by many in this population and the HIV status of our study population is currently unknown. No actual cases of acquired immunodeficiency syndrome in Seattle have been diagnosed among juvenile female prostitutes. As of this time, HIV positivity among adult female prostitutes in the King County Jail is 2% (Hunter Handsfield Office, Harborview Medical Center, Seattle).

Provision of preventive health care and social services to this population is especially difficult. Community-based, case-management approaches are indicated. Health services must be offered

in a manner that builds trust and eliminates access barriers. Health screening and patient education are best provided through an outreach effort that engages these young women in the community, in institutions, and on the street. Liaison with existing adolescent health services is essential to provide needed obstetric services and treatment for sexually transmitted diseases, drug abuse, and physical trauma.

Many of these young women require emotional support and safe shelter during pregnancy to improve pregnancy outcome. Homes for unwed mothers that formerly existed have been closed in an attempt to reduce the stigma, to mainstream this population, and to streamline services. Unfortunately, this forces the young woman to stay with her pimp/boyfriend or to continue prostituting to provide food and shelter.

More study is needed to characterize this growing population and their health problems and needs. Health and social services professionals must become much more aware of the unique problems of these vulnerable adolescents, and training must be provided to improve the capabilities of public health professionals to address them. More must be learned about the infants of these adolescents in terms of developmental status and pediatric health care needs. The problems of the pregnant adolescent engaged in prostitution can no longer be ignored by health professionals. The stakes have become too great for young mothers and their infants.

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Adolescent Contraceptive Use and Parental Notification

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• Little research exists regarding the relationship between family communication and the sexual behavior and contraceptive use of adolescent females. A self-administered questionnaire was used to survey 196 adolescent females regarding communication with their parents about sexual issues and their reaction to proposed parental notification of the dispensing of prescription contraception. Parents of 80% of the subjects who were sexually experienced were aware of this activity. Parents of 80% of those subjects who had used contraception were aware of this use; 59% of these subjects informed their parents before their family planning visit. The majority of female adolescents (57%) were unwilling to communicate with their parents about sexual issues; 64% felt they should be able to receive prescription contraception without parental knowledge. Communication regarding sexual issues was related to lifetime contraceptive use. Eighteen percent of the sexually experienced subjects would not allow their parents to be notified of their family planning visit; 86% would use less effective contraception if family planning services were not sought. Our findings suggest that a parental notification policy will not compel all adolescents to inform parents about their contraceptive use; most adolescents will resort to less effective contraceptive methods.

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Since the early 1970s, a dramatic increase in premarital intercourse among adolescents has occurred. One national survey found that in 1979, 46% of all 15- to 19-year-old females who had

never been married were sexually experienced, compared with 28% in 1971.¹ The risk of premarital pregnancy has similarly risen. In 1984, there were just over 1 million pregnancies and 470 000 livebirths to women younger than 20 years.² Although some 367 000 unplanned pregnancies are stopped annually by federally funded family planning services,³ many more could be prevented if adolescents consistently used contraception.

Adolescents may use contraception less effectively when parents are unaware they are having sexual relations and would disapprove if they knew.^{4,5} Several studies suggest that communication between mothers and their daughters regarding contraception is related to more effective contraceptive practice by the adolescent.⁶⁻⁸

Several states have considered or enacted statutes and one federal agency has attempted to implement regulations in recent years requiring parental notification by agencies that provide prescription contraceptives to unemancipated adolescents. The ensuing debates highlighted the fact that little research exists regarding the relationship between family communication and adolescent use of contraceptive services. One study indicated that 23% of all females younger than 18 years enrolled in a family planning clinic would stop coming and use less effective contraception if such a rule were implemented.⁹ Another study found that 43% of teenage girls attending a family planning clinic for the first time cited fear of parental notification as a major reason for their delay in seeking services.¹⁰

We utilized a self-administered questionnaire to survey a group of adolescent females presenting to a general adolescent medicine clinic regarding their communication with their parents about sexual issues and their reaction to the

proposed parental notification of the dispensing of prescription contraception.

PATIENTS AND METHODS

Unmarried nulliparous female patients 15 to 18 years of age who attended the Adolescent Clinic of Oklahoma Children's Memorial Hospital, Oklahoma City, for health care from February 1983 to December 1983 were eligible to participate in the study. The clinic provides primary care to indigent teenagers 13 to 21 years of age from the Oklahoma City area and offers care to physician- and self-referred patients from throughout the state. A preliminary version of the data collection instrument was piloted with 15 subjects. The instrument was reviewed by two experts in adolescent health care for content and was reviewed by a public health expert experienced in questionnaire design for item construction. No external checks were made regarding the validity of the subjects' responses. Test-retest reliability was not assessed. A convenience sample of 196 subjects was included in the study; 1 patient declined to participate. Written informed consent was obtained; confidentiality was assured. This study was approved by the Institutional Review Board of the University of Oklahoma Health Sciences Center, Oklahoma City.

A self-administered, printed questionnaire was used for data collection. Reading ability was assessed using a paragraph at a sixth-grade level of difficulty. One investigator (E.D.) reviewed the responses with each participant. Demographic information requested included age, ethnicity, religion, parent with whom subject resided, family income, parents' educational level and occupation, city or town of residence, present school attendance, grade appropriateness for age (based on Bureau of the Census criteria), highest grade completed, grade-point average, and reason for the clinic visit. The following sexuality-related information was collected: past and present sexual activity, age at first sexual experience, parents' awareness of sexual activity, past and present contraceptive use, age at first contraceptive use, duration of current contraceptive use, parents' awareness of contraceptive use, and the reason contraceptives were not

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being used. Each subject was also asked to comment on the following: ability to communicate with parents regarding sexuality-related issues, whether teenagers should be able to receive prescription contraception without parental notification, course of action if parental notification were required to receive these services, and the course of action if services that provided contraceptives were not sought. A Hollingshead Two-Factor Index of Social Position was calculated for each subject. This index, based on parents' occupation and educational level, ranged from 1, representing the highest social position, to 5.

Mean and range, or mean \pm 1 SD if the variable were normally distributed, were used as measurements of central tendency. Univariate analysis utilizing the χ^2 and Student's *t* test identified independent variables related to the dependent variable of interest. Because two groups were compared for multiple independent variables, relationships with a $P \leq .01$ were considered significant to reduce type I error. Univariate relationships between independent and dependent variables with a $P \leq .10$ are shown in Tables 1 through 6. These independent variables were used to perform a multiple logistic regression analysis. This analysis incorporates intercorrelations among independent variables and selects those variables that best predict the outcome variable. This regression model is more appropriate for use with dichotomous dependent variables than ordinary least-squares regression. A $P \leq .05$ was considered significant. The regression coefficient β and the *P* value are shown for each significant independent variable. Software was used to perform the data analysis.

RESULTS

Demographic characteristics are given in Table 7. Subjects were a mean of 16.0 ± 1.1 years of age, mainly white (57%), Protestant fundamentalist (81%), and of lower socioeconomic status (56%). Sexuality-related characteristics are given in Table 8. Sixty-five percent were sexually experienced, and 53% were sexually active (defined as sexual activity within the preceding 2 months). Of those who were currently sexually active, 48% were using effective contraception (oral contraceptives, foam, or condoms). The following reasons were given by the 55 subjects who were not using effective contraception: didn't get around to it, 20%; concerned about side effects, 16%; may be or wants to be pregnant, 13%; worried parents would find out, 11%; didn't know where to go, 11%; inconvenient to use, 9%;

Characteristics	Sexually Experienced, No. (%)		<i>P</i>
	Yes*	No	
Subjects	128 (65)	68 (35)	...
Age, y (mean \pm 1 SD)	16.3 \pm 1.0	15.5 \pm 1.0	.0001
Ethnicity			
W	65 (51)	47 (69)	
B	52 (41)	17 (25)	.05
Other	11 (9)	4 (6)	
Resides with			
Both parents	61 (48)	46 (68)	
Other	67 (52)	22 (32)	.008
Income per year			
>\$20 000	37 (30)	27 (42)	
<\$20 000	88 (70)	38 (58)	.09
Hollingshead Index of Social Position, mean (range)	3.7 (1-5)	3.2 (1-5)	.005
Residence			
Oklahoma City proper	83 (65)	34 (50)	
Suburban or rural	45 (35)	34 (50)	.05
Dropped out of school			
No	111 (87)	67 (99)	
Yes	17 (13)	1 (1)	.006
Highest grade completed, mean (range)	9.6 (7-12)	8.6 (5-12)	.0001
Grade-point average			
3.1-4.0	41 (34)	37 (55)	
\leq 3.0	79 (66)	30 (45)	.005
Receive prescription contraception without parental knowledge?			
Yes	91 (71)	33 (49)	
No	37 (29)	34 (51)	.003
If family planning services were not sought, subjects would			
Not have intercourse	14 (11)	39 (57)	
Use barrier methods	80 (63)	28 (41)	.0001
Have unprotected intercourse	34 (27)	1 (1)	

*Percentage may not total 100 because of rounding.

didn't feel contraception was needed, 9%; couldn't afford contraception, 4%; boyfriend objected to contraceptive use, 2%; and no reason given, 6%.

At least one parent of 80% of those teenagers who had used contraceptives was aware of their use. The majority (59%) of teenagers informed their parents before their first family planning visit; 32% reported a parent had accompanied them. The following reasons were given by the 15 responding subjects who had not informed their parents: afraid their parents would be angry, 47%; none of their parents' business, 20%; they had just started us-

ing birth control, 13%; no reason, 13%; and hadn't thought about it, 7%.

A minority of teenagers (43%) felt they were able to communicate with their parents regarding sexual issues; almost two thirds felt they should be able to receive prescription contraception without parental knowledge. Twenty percent of all respondents and 18% of the sexually experienced subjects would not allow their parents to be notified and would not seek family planning services if parental notification were mandatory. Eighty-seven percent of those who would not allow their parents to be notified would remain sexual-

Table 2.—Comparison of Sexually Experienced Subjects Who Had Used Prescription Contraceptives vs Those Who Had Not

Characteristics	Used Prescription Contraceptives, No. (%)		P
	Yes	No	
Subjects	71 (55)	57 (45)	...
Age, y (mean \pm 1 SD)	16.6 \pm 0.9	16.1 \pm 1.1	.01
Dropped out of school			
Yes	14 (20)	3 (5)	.02
No	57 (80)	54 (95)	
Age at first sexual experience, y (mean \pm 1 SD)	14.5 \pm 1.6	15.0 \pm 1.3	.04
Parents' awareness of sexual activity			
Yes	56 (79)	33 (58)	.01
No or not sure	15 (21)	24 (42)	
Willingness to communicate with parents about sexual issues			
Yes	39 (55)	15 (26)	.001
No	32 (45)	42 (74)	
Received prescription contraception without parental knowledge?			
Yes	46 (65)	45 (79)	.08
No	25 (35)	12 (21)	

ly active—56% said they would use barrier contraceptives and 31% said they would have unprotected intercourse. Almost three fourths of all the respondents said they would remain sexually active even if they did not seek family planning services.

Subjects were divided into two groups for further analysis based on previous sexual experience. Demographic factors that correlated with sexual experience are shown in Table 1. Religious background and ability to communicate with parents about sexual issues were not related to sexual experience. Sexually experienced subjects were more likely to feel they should be able to receive prescription contraceptives without parental knowledge and were less likely to refrain from sexual activity should they not seek family planning services. The association between sexual experience and demographic and sexuality-related characteristics was further evaluated using logistic regression analysis. The characteristics significantly related to sexual experience were age ($\beta = .48$, $P = .02$), whether the subject was a school dropout ($\beta = 2.30$, $P = .05$), the Hollingshead

Index ($\beta = .39$, $P = .05$), and willingness to abstain from intercourse if family planning services were not sought ($\beta = -1.97$, $P = .0002$) ($\chi^2 = 60.11$, $df = 10$, and $P < .0001$ for the entire model).

Responses of sexually experienced subjects were examined according to whether these subjects had ever used prescription contraceptives (Table 2). Contraceptive users had parents who were aware of their sexual activity and were willing to communicate with their parents regarding sexual issues. Race, religion, socioeconomic status, school achievement, and age at first intercourse were unrelated to contraceptive use. Only age ($\beta = 1.00$, $P = .0005$), age of first sexual experience ($\beta = -.65$, $P = .002$), and parents' awareness of sexual activity ($\beta = .70$, $P = .03$) were predictive of prescription contraceptive use by logistic regression ($\chi^2 = 32.43$, $df = 6$, and $P < .0001$ for the entire model).

The willingness of subjects to communicate with parents regarding sexual issues was identified as an important outcome (Table 3). Those who were able to communicate were more likely to use

prescription contraceptives and have parents who were aware of their sexual activity and contraceptive use. This group also demonstrated a trend toward the belief that parents should be informed of their visit to a family planning facility before its occurrence ($P = .08$). Age, religion, socioeconomic status, sexual activity, age at first intercourse, age at first contraceptive use, or interval since first contraceptive use were not related to communication. Multivariate analysis revealed that only the belief that adolescents should be able to receive contraception without parental knowledge ($\beta = -1.02$, $P = .01$) and a willingness to notify parents to receive prescription contraceptives ($\beta = 1.64$, $P = .005$) were related to a willingness to communicate ($\chi^2 = 48.12$, $df = 10$, and $P < .0001$ for the entire model).

The second important outcome variable was whether adolescents felt they should be able to receive prescription contraceptives without parental knowledge (Table 4). Those who answered affirmatively were more likely to be sexually experienced, were less willing to communicate with parents regarding sexual issues, and would not allow parents to be notified of their family planning visit. Logistic regression indicated that only a willingness to communicate with parents regarding sexual issues ($\beta = -.80$, $P = .05$), to allow parents to be notified of the family planning visit ($\beta = -3.24$, $P = .003$), and to abstain from intercourse if prescription contraceptives were unavailable ($\beta = -2.38$, $P = .0001$) were related to the outcome measurement of interest ($\chi^2 = 71.18$, $df = 8$, and $P < .0001$ for the entire model).

The willingness of teenagers to inform their parents of their family planning visit was another important outcome measurement (Table 5). Those who would do so were more likely to live in Oklahoma City proper, were willing to communicate with parents about sexual issues, and were less likely to desire prescription contraception without parental knowledge. Logistic regression analysis indicated that only a willingness to communicate with parents about sexual issues ($\beta = 1.79$, $P = .003$) and desire to receive prescription contraceptives without parental knowledge

Table 3.—Willingness to Communicate With Parents Regarding Sexual Issues

Characteristics	No. (%)		P
	Yes*	No	
Subjects	85 (43)	111 (57)	...
Ethnicity			
W	50 (59)	62 (56)	
B	24 (28)	45 (41)	.02
Other	11 (13)	4 (4)	
Dropped out of school			
Yes	12 (14)	6 (5)	
No	73 (86)	105 (95)	.04
Parents aware of sexual activity			
Yes	43 (80)	46 (62)	
No or not sure	11 (20)	28 (38)	.03
Current use of prescription contraception			
Yes	23 (43)	20 (27)	
No	31 (57)	54 (73)	.06
Lifetime use of prescription contraception			
Yes	39 (72)	32 (43)	
No	15 (28)	42 (57)	.001
Parents aware of contraceptive use			
Yes	40 (93)	29 (63)	
No or not sure	3 (7)	17 (37)	.001
Received prescription contraception without parental knowledge?			
Yes	38 (45)	86 (77)	
No	46 (55)	25 (23)	.0001
If parental notification were required for prescription contraceptives, subjects would			
Allow clinic to notify parents	22 (26)	25 (23)	
Notify parents herself	59 (69)	51 (46)	.0001
Not allow parents to be notified	4 (5)	35 (32)	
If family planning services were not sought, subjects would			
Not have intercourse	31 (36)	22 (20)	
Use barrier methods	40 (47)	68 (61)	.03
Have unprotected intercourse	14 (16)	21 (19)	

*Percentage may not total 100 because of rounding.

Table 4.—Should Teenagers Be Able to Receive Prescription Contraception Without Parental Knowledge?

Characteristics	No. (%)		P
	Yes*	No	
Subjects	124 (64)	71 (36)	...
Age, y (mean \pm 1 SD)	16.1 \pm 1.1	15.9 \pm 1.2	.10
Highest grade completed, mean (range)	9.4 (6-12)	9.0 (5-12)	.03
Sexually experienced			
Yes	91 (73)	37 (52)	
No	33 (27)	34 (48)	.003
Current use of prescription contraception			
Yes	25 (27)	18 (49)	
No	66 (73)	19 (51)	.02
Lifetime use of prescription contraception			
Yes	46 (51)	25 (68)	
No	45 (49)	12 (32)	.08
Interval (y) since first contraceptive use, mean (range)	1.2 (0.1-3.3)	0.8 (0.1-2.0)	.05
Parents aware of birth control use			
Yes	44 (72)	25 (89)	
No or not sure	17 (28)	3 (11)	.07
Willingness to communicate with parents about sexual issues			
Yes	38 (31)	46 (65)	
No	86 (69)	25 (35)	.0001
If parental notification were required for prescription contraceptives, subjects would			
Allow clinic to notify parents	29 (23)	18 (25)	
Notify parents herself	57 (46)	52 (73)	.0001
Not allow parents to be notified	38 (31)	1 (1)	
If family planning services were not sought, subjects would			
Not have intercourse	13 (10)	39 (55)	
Use barrier methods	82 (66)	26 (37)	
Have unprotected intercourse	29 (23)	6 (8)	.0001

*Percentage may not total 100 because of rounding.

($\beta = -2.86$, $P = .007$) were related to the outcome variable ($\chi^2 = 40.82$, $df = 7$, and $P < .0001$ for the entire model).

Finally, adolescents who indicated they would have unprotected intercourse if family planning services were unavailable were contrasted with those who would use barrier methods or would abstain from sexual relations (Table 6). Logistic regression indicated that only sexual experience ($\beta = 3.33$, $P = .002$) and a willingness to allow parents to be notified of the family planning

visit ($\beta = -1.20$, $P = .02$) were significantly related to the outcome variable ($\chi^2 = 34.73$, $df = 7$, and $P < .0001$ for the entire model).

COMMENT

Results from our study suggest that the majority of adolescent females who use our clinic would continue to attend if parental notification were required to receive family planning services. However, 18% of sexually experienced adolescents would not allow their parents to

be notified and would not come to the clinic under these circumstances; most patients would remain sexually active and would use less effective methods of contraception or none. The majority of sexually inexperienced subjects indicated they would abstain from intercourse; this finding reflects their inexperience with sexual issues and raises the question whether a parental notification policy might influence adolescents to delay sexual activity.

Parental knowledge of their daugh-

Table 5.—Willingness to Inform Parents About Visit to a Family Planning Facility

Characteristics	No. (%)		P
	Yes*	No	
Subjects	157 (82)	39 (20)	...
City or town of residence			
Oklahoma City proper	100 (64)	17 (44)	.02
Other	57 (35)	22 (56)	
Appropriate grade for age			
Yes	112 (71)	34 (87)	.04
No	45 (29)	5 (13)	
Parents aware of birth control use			
Yes	60 (81)	9 (60)	.07
No or not sure	14 (19)	6 (40)	
Willingness to communicate with parents about sexual issues			
Yes	81 (52)	4 (10)	.0001
No	76 (48)	35 (90)	
Received prescription contraception without parental knowledge?			
Yes	86 (55)	38 (97)	.0001
No	70 (45)	1 (3)	
If family planning services were not sought, subjects would			
Not have intercourse	48 (31)	5 (13)	.02
Use barrier methods	86 (55)	22 (56)	
Have unprotected intercourse	23 (15)	12 (31)	

*Percentage may not total 100 because of rounding.

Table 6.—Intended Action if Family Planning Services Are Not Sought

Characteristics	No. (%)		P
	Have Unprotected Intercourse	Use Barrier Method or Abstain From Intercourse	
Subjects	35 (18)	161 (82)	...
Age, y (mean \pm 1 SD)	16.5 \pm 1.1	15.9 \pm 1.1	.01
Religion			
Protestant fundamentalist	23 (68)	132 (84)	.03
Other	11 (32)	26 (16)	
Dropped out of school			
Yes	7 (20)	11 (7)	.01
No	28 (80)	150 (93)	
Highest grade completed, mean (range)	9.7 (7-12)	9.2 (5-12)	.02
Sexually experienced			
Yes	34 (97)	94 (61)	.0001
No	1 (3)	61 (39)	
Ever used effective contraception			
Yes	19 (56)	70 (74)	.04
No	15 (44)	24 (26)	
Received prescription contraception without parental knowledge?			
Yes	29 (83)	95 (59)	.009
No	6 (17)	65 (41)	
If parental notification were required for prescription contraceptives, subjects would			
Allow clinic to notify parents	7 (20)	40 (25)	.06
Notify parents herself	16 (46)	94 (58)	
Not allow parents to be notified	12 (34)	27 (17)	

Table 7.—Demographic Characteristics of Study Participants (N = 196)

Characteristics	%*
Age, y (mean \pm 1 SD)	16.0 \pm 1.1
Ethnicity	
W	57
B	35
Other	8
Religion	
Protestant fundamentalist	81
Catholic	9
Protestant nonfundamentalist	6
Other	4
Income per year	
<\$10,000	27
\$10,000-\$19,999	39
\$20,000-\$39,999	28
\geq \$40,000	5
Hollingshead Index of Social Position, mean (range)	3.5 (1-5)
Resides with	
Both parents	55
One parent	40
Other relatives or guardians	6
Residence	
Oklahoma City proper	60
Suburban or rural	40
Dropped out of school	9
Highest grade completed, mean (range)	9.3 (5-12)
Appropriate grade for age	75
Grade-point average	
3.1-4.0	42
2.1-3.0	51
\leq 2.0	7
Reason for clinic visit	
Family planning	18
Pregnancy testing	10
Other (routine physical, illness, or follow-up)	72

*Percentage may not total 100 because of rounding.

ters' sexual activity and contraceptive use was high among our study population. This was surprising, given the conservative values of the southwestern United States. Most parents found out about their daughters' contraceptive use directly from them. The majority of teenagers were able to inform their parents of their contraceptive needs before the family planning visit.

The majority of our patients felt they were unable to communicate with their parents regarding sexual issues, and almost two thirds of our patients felt they should be able to receive prescription contraception without parental knowledge. The interval since first contraceptive use and the duration of current contraceptive method use were no longer for those who were able to communicate with parents, suggesting communication does not improve once teenagers begin to use contraception. A larger percentage of those subjects who were

able to communicate with their parents informed them about their visit to a family planning facility before its occurrence, suggesting that preexisting communication may facilitate the initiation of contraceptive use.

Subjects from Oklahoma City were more willing to inform parents of their family planning visit than those from surrounding suburban areas. These less affluent adolescents use the Adolescent Clinic for primary care and may be less secretive with parents regarding sexual issues than adolescents from more affluent suburbs, who often come to the clinic for confidential family planning services.

Our results are similar to those reported by Torres et al,⁹ who found that 23% of teenaged girls attending a family planning clinic would stop doing so if parental notification were required. Twenty percent of our entire study group and 18% of our sexually experienced subjects would not attend. Torres et al⁹ found that only 9% of those who would stop attending would abstain from intercourse and 27% would have unprotected sexual relations. Of our subjects who would not allow their parents to be notified, only 13% would abstain from intercourse and 31% would have unprotected intercourse.

Previous studies indicate that 54% to 67% of parents were aware of their adolescent daughters' family planning visits.^{9,11} We found that a higher percentage of parents (80%) were aware of their daughters' contraceptive use. Furstenberg et al¹¹ reported that 56% of mothers found out about their daughters' contraceptive use before or at about the time of the first family planning visit; this is similar to our finding of 59%.

The study of Furstenberg et al¹¹ also found that those who informed their parents about their contraceptive use early on did not communicate more effectively about sexual issues. This contrasts with our data, which demonstrated a trend toward such a relationship. Furstenberg et al¹¹ reported that 39% of the adolescents attending a family planning clinic were able to communicate with their parents regarding sexual issues; we found 43% of our relatively unselected subjects could do so. We had expected better communication since it is those adolescents who

Table 8.—Sexuality Related Characteristics of Study Participants (N = 196)

Characteristics	%*	95% Confidence Interval
Sexual behaviors		
Sexually experienced	65	58-72
Currently sexually active	53	46-60
Age of first sexual experience, y (mean \pm 1 SD)	14.7 \pm 1.5	14.4-15.0
Parents aware of sexual activity (N = 128)	70	62-78
Contraceptive behaviors of sexually experienced subjects (N = 128)		
Age (y) at first use of contraception, mean (range)	15.4 (13.5-17.3)	15.2-15.6
Interval (y) since first contraceptive use, mean (range)	1.1 (0.8-3.3)	0.9-1.3
Lifetime use of contraception		
Oral contraceptives	56	47-56
Condoms	21	14-28
Withdrawal	8	2-10
Foam	4	1-7
Rhythm	4	1-7
Foam and condoms	2	0-4
Lifetime use of effective contraception	70	62-78
Method of contraception used by currently sexually active subjects (N = 104)		
Oral contraceptives	35	26-44
Condoms	9	3-15
Foam	2	0-5
Foam and condoms	2	0-5
Withdrawal	2	0-5
Rhythm	1	0-3
Nothing	50	40-60
Duration (mo) of current method use, mean (range)	8.4 (0-39)	6.1-10.7
Parents' awareness of contraceptive use (N = 86)	80	72-88
How did parents find out (N = 66)		
Subject told parents prior to clinic visit	59	47-71
Subject told parents after clinic visit	33	22-44
Parents found out from someone else	8	1-15
Attitudes		
Willing to communicate with parents about sexual issues	43	36-50
Teenagers should be able to receive prescription contraception without parental knowledge	64	56-71
Intended course of action of subjects if parental notification were required to receive prescription contraception		
Notify parents herself	56	49-63
Allow clinic to notify parents	24	18-30
Not allow parents to be notified	20	14-26
Intended course of action of subjects if patient decided not to seek family planning services		
Not have intercourse	27	21-33
Use barrier methods	55	48-62
Unprotected intercourse	18	13-23

*Percentage may not total 100 because of rounding.

desire confidential services that most often use family planning clinics. Finally, these investigators showed that black teenagers reported better communication than white teenagers.¹¹ However, we found that blacks were least likely to communicate with parents about sexual issues.

Our findings of a positive association between parent-daughter communication and use of effective contraception are similar to other published results.⁶⁻⁸ A more recent study failed to demonstrate a relationship between continuous contraceptive use and effective communication.¹¹ Additional studies are necessary to delineate further the determinants of parent-daughter communication regarding sexual issues and to identify better the relationship between communication patterns and the commencement and continuation of effective contraception by teenagers.

An important limitation of our study is that parents were not interviewed regarding communication with their daughters about sexual issues or their

knowledge of their daughters' sexual behaviors. The perceptions of adolescents regarding these issues may differ considerably from those of their parents. Additionally, our findings are specific to a group of largely inner-city youth from a southwestern city and may not be generalizable to adolescents residing in other parts of the United States.

Our findings have significant implications regarding state and federal efforts to impose parental notification requirements on minors seeking contraceptive services. Although these findings suggest that parent-adolescent communication regarding sexual issues may facilitate the use of effective contraception, such communication seems to predate the visit to a family planning facility and probably cannot be created by legislative or regulatory means. A parental notification policy will not obligate all adolescents to inform their parents about their contraceptive use or stop them from having sexual relations. The end result may well be an increase

in the use of less effective contraception and unintended pregnancy. Parental involvement should be encouraged by family planning agencies where appropriate. Research suggests that clinics that encourage, rather than require, teenagers to inform their parents of their attendance have a significantly higher level of parental involvement.¹²

We found that most parents were aware of their adolescent daughters' sexual activity and contraceptive use. Communication between parents and daughters regarding sexuality was less prevalent. If parental notification were required to receive family planning services, a small but significant percentage of respondents indicated they would not attend our clinic and would resort to less effective contraceptive methods.

The software used to perform the data analysis in this study was supplied by SAS Institute Inc, Cary, NC.

Herbert L. Kayne, PhD, gave advice regarding the statistical analysis, and Patricia M. Demers, MS, MPH, provided editorial assistance.

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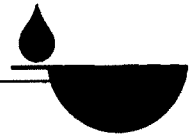
Otitis Media: Incidence, Duration, and Hearing Status

Peter S. Roland, MD; Terese Finitzo, PhD; Sandy Friel-Patti, PhD; Karen Clinton Brown, MS; Kay T. Stephens, MD; Orval Brown, MD; J. Michael Coleman, PhD
(*Arch Otolaryngol Head Neck Surg.* 1989;115:1049-1053)

Combined Effects of Aspirin and Noise in Causing Permanent Hearing Loss

Shannon S. Carson, MSIV; Jiri Prazma, PhD; Stephen H. Pulver; Travis Anderson
(*Arch Otolaryngol Head Neck Surg.* 1989;115:1070-1075)

Educational Interventions



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Purpose.—This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.

Editorial Comment.—*How well do we train our future colleagues to manage their patients with insulin-dependent diabetes mellitus, a common and serious disease? The model presented here, including its reminder system, apparently did not work. Any suggestions?*—H.D.A.

Management of Diabetes in Pediatric Resident Continuity Clinics

Kathleen K. Kronz; Roberta Ann Hibbard, MD; David G. Marrero, PhD;
Gary M. Ingersoll, PhD; Naomi S. Fineberg, PhD; Michael P. Golden, MD

• General pediatricians provide comprehensive care for many children with insulin-dependent diabetes mellitus. To assess and improve our ambulatory training program, we first evaluated diabetes-specific care behaviors by residents in their continuity clinics and then introduced a structured visit encounter form. Based on established guidelines provided to the residents, a chart audit indicated appropriate measurement of glycosylated hemoglobin 40% of the time, cholesterol 90% of the time, urine protein 50% of the

time, and thyroxine 66.7% of the time. Height was plotted 23% of the time, blood pressure was noted 66% of the time, and ophthalmologic referrals were documented 60% of the time. Requests for assistance from nonphysician members of a multidisciplinary diabetes team were minimal. After introduction of the structured visit encounter form, care behaviors did not improve. New training approaches to prepare general pediatric residents to provide excellent diabetes care are needed. (AJDC. 1989;143:1173-1176)

Insulin-dependent diabetes mellitus (IDDM) is one of the most common childhood chronic illnesses, affecting 1.8 of 1000 children aged 0 to 20 years.¹ Most general pediatricians, therefore, will encounter patients with IDDM regularly, and indeed several surveys²⁻⁴

suggest that general pediatricians in the United States provide a substantial portion of the medical care for children with IDDM. The typical pediatrician provides either complete or shared medical care to a median of 4 patients with IDDM.² Hence, for general pediatric training programs to provide adequate preparation, they need to include substantial experience in the outpatient care of patients with IDDM.

Published guidelines for training in general pediatrics call for inclusion of ambulatory training in diabetes care,⁵ and the majority of pediatric residency

programs include longitudinal IDDM care by residents.² A portion of this training at our center is accomplished in the general pediatric resident ambulatory care clinics (continuity clinics). In this setting, the resident has primary responsibility for his or her patients and reviews decisions with a general pediatric preceptor who is present at the clinic. Involvement in the care of these patients by diabetes team members, including endocrinologists, nurse practitioners/educators, dietitians, and social workers, is at the discretion of the resident and preceptor. Therefore, the continuity clinic is an appropriate site for evaluating the diabetes-related care practices of residents. Similarly, it provides a setting where specific interventions to improve care and/or training can be evaluated.

Under the auspices of the Indiana University Diabetes Research and Training Center, we have begun a series of studies designed to evaluate training of general pediatric residents in the continuity clinic setting. As a preliminary step, we conducted a chart audit of patients followed up in the conti-

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Reprints not available.

nuity clinics to determine the extent to which residents were following current care guidelines. The results, discussed below, documented deficiencies in adherence to several areas of patient care guidelines, thus indicating a need for intervention.

Previous investigations have shown that reminder systems incorporated into either charts or databases have increased residents' adherence to recommended care guidelines.^{6,8} A study at our center found that a computerized reminder system available to general internal medicine residents increased residents' adherence to preventive health care guidelines.^{6,7} This type of system was not available, however, in the pediatric continuity clinics; nor is it generally available nationally in either training or practice settings. To develop an analogous intervention that could be easily applied in a variety of settings, we created a structured IDDM visit encounter form for residents.

Increased compliance with American Academy of Pediatrics' guidelines for physician care activities and data recording behaviors has been demonstrated with the use of a structured age-oriented patient encounter form.⁸ Based on this work, we hypothesized that by providing a visit flow sheet outlining care guidelines on which data collected during the clinic visit are recorded, residents would be immediately reminded of recommended care guidelines, and thus adherence to these guidelines would improve. Our report describes the implementation and evaluation of this intervention.

MATERIALS AND METHODS

Resident Training

Residents caring for patients with diabetes in their continuity clinics were responsible for comprehensive care of one or two children. Each resident was given a diabetes handbook that provided guidelines for insulin and dietary management, the approach to treatment of patients in poor metabolic control with or without recurrent ketoacidosis, appropriate monitoring for metabolic control, screening and treatment of risk factors, such as hypertension and hyperlipidemia, diabetic complications, guidelines for obtaining physical and laboratory measurements, psychosocial issues of diabetes, and patient education. Several lectures each year dealt with inpatient and outpatient management, including review of the guidelines in the

handbook. Most second-year or third-year residents participated on the endocrine service, which involved inpatient and outpatient IDDM management and close interaction with a multidisciplinary team. Portions of the clinical care program have been described previously.^{9,10}

Development of the Structured Visit Encounter Form

A structured IDDM visit encounter form was developed to serve educational and data collection functions, as well as to provide residents with algorithms for laboratory and physical evaluation. The final form was agreed on by all members of the multidisciplinary team and two general pediatricians. Questions were divided into four categories: patient history, diabetes-specific physical findings, laboratory tests to be ordered with results from the previous visit, and the physician's evaluation and plan. Included in the history were questions pertaining to insulin adjustment, diet, exercise, and psychosocial issues.

Reminders of the appropriate frequency of laboratory tests, guidelines for obtaining further tests, and checklist opportunities for psychosocial, educational, and dietary referrals were also included. Guidelines for the optimal frequency of evaluations were those listed in the physician's diabetes handbook. Results of blood glucose self-monitoring were to be evaluated at every visit. Blood pressure, height (for patients under 14 years of age), and weight measurements were to be obtained every 3 months and plotted on a growth chart. Glycosylated hemoglobin measurements were to be obtained every 3 months. Serum cholesterol, serum thyroxine, and urine protein levels were to be measured at least yearly. An ophthalmology referral was recommended yearly for patients with diabetes of greater than 5 years' duration. These recommendations preceded and are similar to the recently published guidelines of the American Diabetes Association.¹¹

After the baseline evaluation of diabetes care, the structured visit encounter form was formally introduced into the continuity clinic setting. A memo was distributed to all residents directing them to use the form with their diabetic patients. Forms were placed in the charts of all diabetic patients at each visit by clinic personnel.

Evaluation

Charts of 30 patients followed up by 23 residents were audited for the period before the introduction of the structured visit encounter form to assess the level of care provided by the residents in their continuity clinics. The period covered was 9 months from October 1, 1985, to June 30, 1986. Tests

and referrals recommended annually were audited back 3 months to July 1 to encompass 1 year's duration. The audit form was used to record whether glycosylated hemoglobin, urine protein, serum thyroxine, or cholesterol measurements had been performed. Referrals to the ophthalmology department and documentation of routine care, including the plotting of height on a growth chart and the measuring of weight and blood pressure, were also included in the audit. In cases where there was no written physician order but there was a laboratory result in the chart or documentation of a visit to the ophthalmology department, it was recorded as if the physician had ordered the test or made the referral.

After the introduction of the encounter form, charts of 45 patients followed up by 29 residents were audited using the same methods and same audit form as was used in the baseline audit. The period was from October 1 through June 30 of the year following the initial audit. Again, annual laboratory tests and ophthalmology department referrals were audited back 3 months for a total 1-year evaluation period. Laboratory values, referrals, and height, weight, and blood pressure determinations not documented on the encounter form but documented elsewhere in the chart were included in the audit as if they had been documented on the patient encounter form.

Analysis

Adequacy of care was assessed by the frequency with which documentation existed to demonstrate that residents reviewed blood glucose results, obtained relevant physical findings, ordered appropriate tests, made ophthalmology referrals within the period recommended, and made referrals to multidisciplinary diabetes team members. The frequencies of these recommended behaviors were compared before and after introduction of the encounter form using Fisher's Exact Test.

Metabolic control was assessed by total stable glycosylated hemoglobin levels (normal, 4.6 to 8.0).¹² Mean glycosylated hemoglobin levels were calculated for each patient and audit period. Significance in glycosylated hemoglobin decrease was determined using a paired *t* test.

RESULTS

Frequencies of resident compliance with care recommended at 3-month and yearly intervals are shown in Table 1. Frequencies of referrals to diabetes team members are shown in Table 2. Before the encounter form was introduced, self-monitored blood glucose levels were documented, and a weight

Table 1.—Frequency of Recommended Resident Behaviors Before and After Introduction of the Structured Encounter Form*

	Diabetes Management		P†
	Before Form	After Form	
Yearly			
Cholesterol levels measured	90	66.7	.027
Urine protein values measured	50	55.6	.814
Ophthalmology referral	60	55.6	.813
Thyroxine levels measured	66.7	68.9	.999
Every visit			
Blood pressure measured	66	46.7	.012
Height plotted	23	27	.837
Weight noted	100	99	.601
Home blood glucose results reviewed	100	99	.999
Glycosylated hemoglobin levels measured	40	46.7	.639

*Values are given as percents.

†Significance was measured using Fisher's Exact Test.

Table 2.—Referrals Made to the Multidisciplinary Diabetes Team Members by Pediatric Residents for All Visits During the Respective Audit Periods

	No. of Referrals		P*
	Before Audit (n=30) (Total Visits=81)	After Audit (n=45) (Total Visits=107)	
Diabetes nurse practitioner	7	9	.999
Dietitian	5	9	.592
Diabetes social worker	7	11	.805
Child psychiatrist	5	3	.294
Diabetes clinic (Endocrinologist)	2	2	.999

*Significance was measured using Fisher's Exact Test.

measurement was plotted at nearly every visit. However, glycosylated hemoglobin levels were measured only 40% of the time, and height was plotted even less often. For yearly actions, cholesterol levels were usually appropriately measured, but other actions were not taken up to 50% of the time. After introduction of the encounter form, no improvement occurred. In fact, the frequency with which blood pressure values were obtained and cholesterol levels measured actually decreased. While our sample size was small, there were no differences in behaviors among first-, second-, or third-year residents. Mean glycosylated hemoglobin level was 12.2% at baseline and 11.5% after

introduction of the encounter form (not significant). Table 2 indicates the number of documented referrals to diabetes team members. Although no specific guidelines are given, the level of the patient's metabolic control indicated by glycosylated hemoglobin values indicates a need for more intervention than was documented. No significant increase in referrals occurred after the introduction of the form.

COMMENT

Baseline chart audits of pediatric residents' care of children with IDDM revealed shortfalls in preferred diabetes care. Based on recommendations provided to the residents, urine protein

was measured 50% of the time, ophthalmology referrals occurred 60% of the time, serum thyroxine was measured 66.7% of the time, blood pressure was measured 66% of the time, height was plotted 23% of the time, and glycosylated hemoglobin was measured 40% of the time.

Documented referrals to the multidisciplinary diabetes team members were also minimal considering the level of metabolic control exhibited by the patients. Residents in our program are exposed to a set of educational interventions that are at least as and perhaps more comprehensive than the IDDM training in many general pediatric programs.² We, therefore, feel that our resident sample was representative of trainees across the country. Thus, these baseline data indicate a need for improved instruction of pediatric residents.

The introduction of a structured visit encounter form is potentially a minimally intrusive, cost-effective mechanism that would serve to remind pediatric residents about needed care. The availability and presence of the structured visit encounter form, however, did not lead to improved diabetes care. Chart audits undertaken after the intervention revealed no improvements in reported referrals and preferred tests. Indeed, evidence was found of possible decay in quality on two measures.

It is possible that the pediatric residents did, in fact, engage in the desired behaviors but failed to record the information in patients' charts. Because the charts were searched for the presence of laboratory reports even when a request was not recorded, and no significant discrepancy was found, this seems unlikely. Furthermore, other studies^{13,14} have demonstrated a high degree of correspondence between actual care and care as recorded in charts.

The reason that availability of a structured encounter form reminder system did not improve pediatric residents' care behaviors is not altogether clear when looking at the success of other seemingly similar interventions⁶⁻⁸; however, it may be due in part to several differences between the interventions. Ertel and Ertel⁸ observed increased compliance with American Academy of Pediatrics' guidelines for physician care

activities and data recording with the use of a structured, age-oriented patient encounter form. The introduction of this form, however, was paired with a tape recording of the patient-physician visit. Although our residents were informed at the beginning of the study that medical record audits of the charts of their patients with IDDM would be performed, with the exception of the presence of the encounter form in the chart, no ongoing reminders were present. Resident care behaviors also improved after the introduction of a computerized medical records reminder system.^{6,7} The computer reminder system also differed in several important ways from our intervention. The computerized system provided the resident with test results from the patient's previous visit and indicated appropriate action to be taken. Our form contained a space on the first page for laboratory results from the previous visit, but the resident was responsible for retrieving and recording these laboratory values from elsewhere in the chart or from the laboratory. The computerized system indicated whether a laboratory result recommended at a certain interval was due to be obtained. The encounter form indicated the frequency with which laboratory results should be obtained; however, it did not provide the resident with the date the laboratory results were previously obtained.

Operational barriers may partially explain why there was not an increase in the number of referrals to diabetes team members.¹⁶ Members could be called at the time of the clinic visit for a consultation but might not be immediately available. If so, the patient had to schedule an appointment at another time. Although similar to what would happen in most practice settings, it is inconvenient for the patient, takes extra time and effort from the resident, and therefore becomes a barrier to referral. In the same fashion, an alteration of the operational setting probably leads to diminished compliance with recording blood pressures. Before the introduction of the structured encounter form,

nurses were responsible for measuring and recording blood pressures. After introduction of the form, nurses were instructed to allow the resident to complete the form. It is possible that nurses assumed that the residents were measuring and recording blood pressure while residents assumed nurses did so. It is important to note that although blood pressure was not measured half of the time, residents failed to follow up on this despite the increased risk of cardiovascular and renal complications associated with diabetes.

We are currently evaluating a more intensive intervention to address the following issue: specifically, implementation of a clinic system that facilitates interaction with a diabetes nurse educator, diabetes social worker, and dietician in the ongoing care of patients. The intent is to provide a care environment in which operational barriers are addressed and minimized.

Finally, caution must be exercised in concluding that failure of pediatric residents to engage in these processes results in poorer metabolic control of the patients.^{16,17} Process variables (laboratory tests ordered, referrals, etc) are important only inasmuch as they lead to adjustment of the treatment regimen. Factors other than physician care, including patient behaviors and the patients' psychosocial environment, contribute to quality of metabolic control.


In summary, our findings indicate that general pediatric residents in their continuity clinics do not demonstrate recommended IDDM care behaviors. The introduction of a reminder system in the form of a visit encounter form to be used at each visit did not increase the frequency of recommended behaviors. In view of the vast participation by general pediatricians in the care of children with IDDM, new training approaches that prepare general pediatricians to provide excellent care for children with IDDM are indicated.

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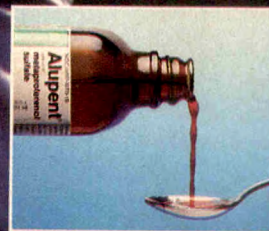


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Reye's Syndrome

A Reappraisal of Diagnosis in 49 Presumptive Cases

Marie Gauthier, MD; Joanne Guay, MD; Jacques Lacroix, MD; Anne Lortie, MD

• We retrospectively studied 49 patients who were discharged from Sainte-Justine Hospital, Montreal, Canada, or who died between 1970 and 1987 with a presumptive diagnosis of Reye's syndrome. Reye's syndrome was defined as certain, probable, unlikely, or excluded according to clinical, biological, and histologic criteria agreed on a priori by a panel of experts. Patient charts were reviewed blindly by three clinicians. Assessments were similar in 42 cases (86%) (weighted $\kappa = 0.78$ to 0.85 , which suggested substantial agreement); for the remainder, agreement was reached after discussion. Reye's syndrome was considered certain in 1 case (2%), probable in 11 (22%), unlikely in 21 (43%), and excluded in 15 (31%). Four children in the study group did not undergo biopsy or autopsy; in three of these, Reye's syndrome was unlikely according to clinical and biological criteria, and in one, the diagnosis was unclassifiable. The incidence of certain or probable Reye's syndrome was low in our institution during the study period. Our results suggest that the apparent disappearance of Reye's syndrome should be reassessed.

(*AJDC*. 1989;143:1181-1185)

Since its description in 1963,^{1,2} Reye's syndrome (RS) has gained wide acceptance as a distinct clinical and pathologic entity. Despite heightened awareness of the existence of this illness, there has recently been a significant decrease in the reported incidence of RS in the United States,³ as well as in Europe⁴ and Australia.⁵ Between January 1985 and May 1986, a prospective study on

the possible relation between RS and medication was performed in the United States, involving 70 pediatric tertiary care centers.⁶ During a period of 18 months, only 27 cases of RS were identified. In recent years, it appears that RS has become a rare disease.

Considering the significant mortality rate associated with RS,^{7,8} this apparently decreasing incidence is particularly interesting to study. To explain why this is occurring, it would help to understand the cause of RS, which is still unknown; it may also help epidemiologists to predict resurgences and perhaps aid physicians in preventing future cases of this disease.

Arrowsmith et al⁹ reported that aspirin use in children and the incidence of RS decreased quite similarly in the United States from 1980 to 1985. This supported the hypothesis that aspirin exposure was a risk factor in the pathogenesis of RS. However, during the same period, the differential diagnosis of RS became broader, as new infections and metabolic diseases mimicking RS were described in the literature.¹⁰⁻¹⁷ It is hypothesized that some acute encephalopathies identified as RS a decade ago would now be diagnosed differently, thus potentially modifying the past incidence of RS. To test this hypothesis, we retrospectively studied the records of patients diagnosed as having RS in our institution since 1970.

PATIENTS AND METHODS

Sainte-Justine Hospital, Montreal, Canada, is a tertiary care pediatric hospital with over 500 pediatric beds, and is staffed by University of Montreal faculty and residents. The charts of all children discharged from Sainte-Justine Hospital after a first episode of RS, or who died with this presumptive diagnosis, between January 1, 1970, and December 31, 1987, were reviewed. Patients

were excluded if transferred to our institution from any other hospital more than 48 hours after their initial admission.

The data collected included age, sex, clinical history before admission, initial assessment (blood pressure, state of consciousness, and response to painful stimuli), laboratory data on admission (creatinine level, cerebrospinal fluid cytologic measurements, and biochemical data) and during the first 48 hours after admission (aspartate aminotransferase, alanine aminotransferase, and ammonia levels), peak bilirubin level during their clinical course, urinary organic acid and serum carnitine levels, results of light and electron microscopy of the liver (when available), and results of the autopsy, when performed.

Clinical Staging

Patients were classified retrospectively according to neurologic assessment on admission. A six-level staging system was used¹⁸: stage 0, alert, wakeful; stage I, difficult to arouse, lethargic, and sleepy; stage II, delirious, combative; stage III, unarousable, predominantly flexor motor responses, or decorticate; stage IV, unarousable, decerebrate; and stage V, unarousable, flaccid paralysis, areflexia, and unresponsive pupils.

Case Definition

Initially, we consulted four experts, including a pediatric gastroenterologist, a pediatric neurologist, a pediatrician with at least 10 years of experience in the care of critically ill children, and a geneticist. They were asked to choose from a list of clinical, biological, and histologic criteria—the criteria that they would use at the time of the study to classify a presumptive case of RS as certain, probable, unlikely, or excluded. They were also asked to give differential criteria for patients younger or older than 12 months of age, and to suggest other criteria if the list was judged incomplete. Second, we summarized the various opinions of the experts, and finally established the definitions described below. There was a consensus of opinion on the final definitions by all experts.

A presumptive case was classified as certain or probable according to criteria listed in

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Presented in part at the 17th Annual Society of Critical Care Medicine Symposium, Orlando, Fla, June 1, 1988.

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Table 1.—Diagnostic Criteria Used to Classify a Presumptive Case of Reye's Syndrome as Certain or Probable*

	Certain		Probable	
	Age ≥12 mo	Age <12 mo	Age ≥12 mo	Age <12 mo
Clinical history				
Consistent with Reye's syndrome	+	—	+	—
Increased AST/ALT levels	+	+	+	+
Increased ammonia level	+	+	+	+
Threefold or greater rise in AST/ALT or ammonia levels	+	+	+	+
Total bilirubin level <51 μmol/L	+	+	+	+
Organic acid levels compatible with Reye's syndrome	—	+	—	—
Normal serum carnitine level	—	+	—	—
No other obvious explanation for the acute illness	+	+	+	+
Hepatic steatosis	+	+	+	+
Mitochondrial alterations compatible with Reye's syndrome	+	+	—	—

*Plus sign indicates that criterion must be present; minus sign, that criterion may be found but is not essential for diagnosis; AST, aspartate aminotransferase; and ALT, alanine aminotransferase.

Table 1. The clinical history was considered compatible with RS if prodromal illness (only required if stage 0 or I) was followed by protracted vomiting with or without progressive alteration of consciousness. In a child less than 12 months of age, the criteria differed compared with older children: a clinical history consistent with RS was not required, and for cases classified as certain, urinary organic acid levels had to be compatible with RS,¹⁹ and serum carnitine level had to be normal.

The occurrence of RS was considered unlikely (1) if two or more of a list of eight characteristics were present (Table 2) (myocardial damage had to be documented by altered contractility, echocardiography, or cardiogenic shock; shock on admission was defined as arterial hypotension with systolic blood pressure at least 30 mm Hg lower than normal) or (2) if the RS was not certain, probable, or excluded. Reye's syndrome was excluded if one of the findings defined in Table 2 was present.

Chart Review

All charts were analyzed independently by three of us, two pediatric intensivists (M.G., J.G.) and a neurology fellow (A.L.). Results were combined from this parallel study. If the reviewers disagreed, a consensus was reached after discussion.

For statistical purposes, we quantified the degree of agreement achieved in the ratings of RS. The concordance of the different raters was expressed in two ways. First, the number of exact agreements for diagnostic categories was noted and cited as a percentage agreement score among the cases stud-

ied. Second, a weighted κ was calculated using the method reported by Kramer and Feinstein.²² This score indicates interobserver agreement with ordinal data. Disagreements were weighted as 1 for a disagreement of one categorical rank, 2 for two ranks, and 3 for three ranks. The strength of interobserver agreement was considered greater than that expected by chance if the value of the weighted κ was higher than the quantitatively significant level of +0.5. To test the null hypothesis that weighted $\kappa = 0$, we calculated an SEM, providing that the total number of cases was greater than $2g^2$, where g is the number of categories; this SEM was used to compute P values to test the null hypothesis. A $P < .05$ (one-tailed test) suggests that the agreement could not be expected by chance only.

RESULTS

Fifty-three patients were diagnosed as having first episodes of RS, either at discharge from the hospital or as cause of death during the 18-year period studied. Four were excluded before analysis because they were transferred to our hospital from 2 to 21 days after admission to a first hospital.

Of the 49 presumptive cases of RS studied, 47% (23/49) of the patients were younger than 12 months at the time of presentation, 25% (12/49) were between 1 and 4 years of age, 18% (9/49) were between 5 and 9 years of age, and 10% (5/49) were between 10 and 14 years of age (Fig 1). The mean age was

Table 2.—Diagnostic Criteria Used to Classify a Presumptive Case of Reye's Syndrome as Unlikely or Excluded*

Reye's syndrome was considered unlikely if the case was not already classified as certain, probable, or excluded, or if two or more of the following characteristics were present:

1. Total bilirubin level ≥ 51 μmol/L
2. Normal ammonia level (if stage 2 or beyond)
3. A threefold or greater rise in creatinine level
4. Focal neurological signs
5. Myocardial damage
6. No prodromal illness (if ≥ 12 months of age)
7. Shock on admission
8. CSF protein level >0.5 g/L

Reye's syndrome was considered excluded if one of the following characteristics was present:

1. Normal AST/ALT²⁰
2. Necrosis and inflammation on liver biopsy²⁰
3. No steatosis²⁰
4. No significant mitochondrial alterations on electron microscopy²¹
5. $>2.5 \times 10^9$ /L
6. Other identified cause for the acute illness

*CSF indicates cerebrospinal fluid; AST, aspartate aminotransferase; and ALT, alanine aminotransferase.

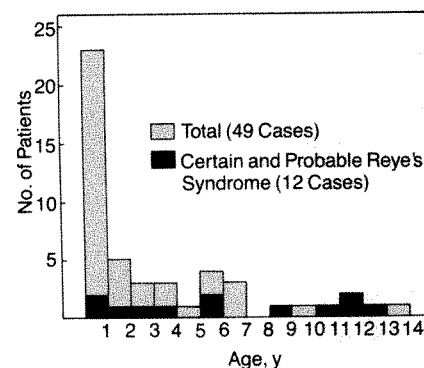


Fig 1.—Distribution of cases of Reye's syndrome at Sainte-Justine Hospital, Montreal, Canada, according to age.

3.2 years (range, 1 month to 13 years 1 month; median, 19 months). The sex proportion was 71% boys and 29% girls. Two percent (1/49) were classified on admission as having stage 0 disease, 25% (12/49) as stage I, 20% (10/49) as stages II and III, 27% (13/49) as stage IV, and 6% (3/49) as stage V. Thirty-three percent (16/49) of the children died during their hospitalization.

Histologic reports were available in 92% (45/49) of patients. Ninety-one per-

Table 3.—Certitude of Diagnosis in 49 Presumed Cases of Reye's Syndrome

	Classification at First Attempt	Classification After Discussion	Total (%)
Certain	...	1	1 (2)
Probable	8	3	11 (22)
Unlikely	20	1	21 (43)
Excluded	14	1	15 (31)
Unclassified	...	1	1 (2)

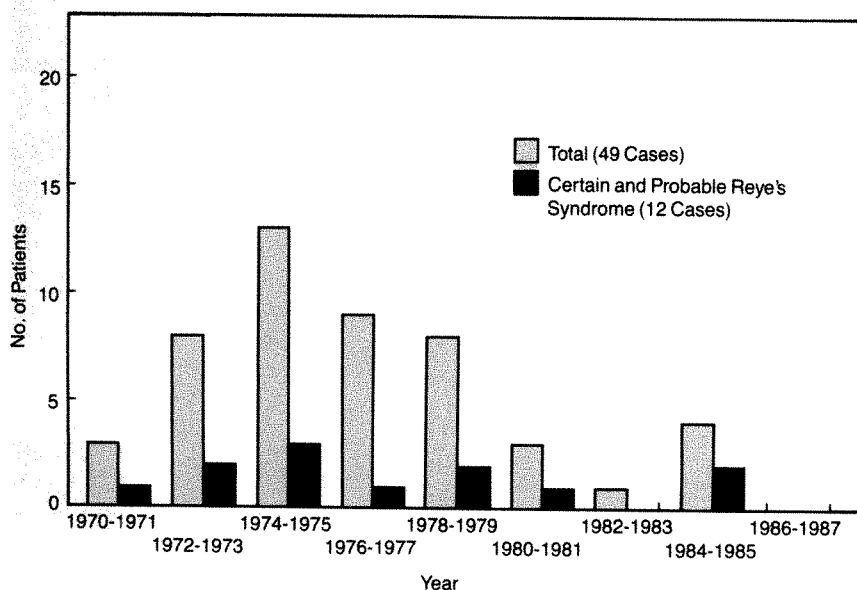


Fig 2.—Incidence of Reye's syndrome at Sainte-Justine Hospital, Montreal, Canada, from 1970 to 1987.

cent (41/47) of these patients had a liver biopsy performed soon after admission, and in 9% (4/45), histologic specimens were taken only at autopsy. Electron microscopy was available for three cases; one of these studies showed typical mitochondrial alterations, the second one showed minimal mitochondrial swelling, the endoplasmic reticulum being the most altered, and the last did not reveal any mitochondrial abnormality.

All three of the reviewers agreed in 12 (86%) of the 49 cases (86% is thus the percentage agreement score). Two disagreements exceeded one category of rank. Three comparisons were performed between the three observers, as suggested by Kramer and Feinstein.²² The weighted κ was higher than the quantitatively significant level of +0.5 or all three comparisons (weighted $\kappa = 0.78, 0.85, \text{ and } 0.83$). The z scores were 5.57, 5.75, and 7.5 ($P < .00003$ in each instance), which again suggested

that the agreements could not be expected by chance alone. These results validate the procedure, because classifying the cases in four categories seems to be reproducible and stochastically significant.

Table 3 shows the results of the parallel diagnostic classification done by three of us. Twelve patients were classified as having certain ($n = 1$) and probable ($n = 11$) RS. They were significantly older, compared with the rest of the group (Fig 1) (mean age, 6.1 years; range, 3 months to 12 years 7 months) vs 2.2 years (range, 2 months to 13 years 1 month) ($P < .001$). Two of these 12 patients were less than 12 months of age at the time of diagnosis, while 21 of the 37 other children studied were in this age group (17% vs 57%, $P < .05$).

Twenty-one presumptive cases (43%) were considered unlikely. In five, the charts were not classifiable either as certain, probable, or excluded; there-

fore, they were categorized as unlikely. Most cases (16 of 21) were classified as unlikely because two or more of the following characteristics were found: shock on admission (8 of 16), cerebrospinal fluid protein level greater than 0.5 g/L (13 of 16), a threefold or greater rise in creatinine level on admission (4 of 16), no prodromal illness in patients older than 12 months (1 of 16), and total bilirubin level of 51 $\mu\text{mol/L}$ (1 of 16). In 9 of the 21 cases classified as unlikely, an alternative diagnosis appeared more likely: viral encephalitis (4 of 21), septic shock (3 of 21), and hypovolemic shock due to gastroenteritis (2 of 21).

In 15 presumptive cases, a diagnosis of RS was excluded. In 11, the final histologic report was not compatible with RS: hepatic tissue necrosis on light microscopy was seen in 6, hepatic inflammation in 2, no significant mitochondrial alterations on electron microscopy in 2, and absence of hepatic steatosis in 1. In all these cases except 1, nothing other than hepatic steatosis was mentioned on the preliminary pathologic reports; final interpretations were sent directly to the charts several days or weeks after the acute disease, almost always after discharge or death of the patients. We considered these 11 cases in retrospect to be drug-induced hepatitis in 1, hepatitis of unknown cause in 1, septic shock in 2, probable adenovirus type 3 systemic infection in 1, severe gastroenteritis with hypovolemic shock in 1, acyl-CoA dehydrogenase deficiency (identified after recurrences) in 2, and acute illnesses of unknown cause in 2. For the last 4 cases excluded, reasons for the exclusion were as follows: proved adenovirus type 7 multisystemic infection, aseptic meningitis, cerebral astrocytoma found at autopsy in a patient who was brain dead on admission, and head trauma in a battered child. Of the 4 children in whom biopsies or autopsies were not performed, 3 were classified as unlikely RS according to clinical and biological criteria, and 1 was judged unclassifiable (Table 3).

The reasons for disagreement among observers were as follows: in three patients, the clinical history was judged compatible with RS by one or two of the observers and not compatible by the other(s); after discussion, these cases were classified as certain in one patient and unlikely in two. One case was

thought to be caused by dimenhydrinate poisoning by one of the observers but was classified as probable after discussion. Another was judged to be an adenovirus type 7 multisystemic infection by one observer. However, the two other observers had not considered this possibility: this case was classified as excluded. Finally, one case was categorized as unclassifiable because of insufficient information (no liver biopsy, spinal tap, or brain biopsy was performed).

Figure 2 shows the incidence of RS in our institution since 1970. Of the 12 patients classified as certain or probable, 6 were admitted during the first 6 years of the study (1970 to 1975), 4 were treated from 1976 to 1981, and 2 were diagnosed over the last 6 years (1982 to 1987). The incidence of these cases remained low during the 18 years of the study.

COMMENT

Of the 49 presumptive cases studied, only 24% (12/49) were considered certain or probable. Because criteria used to classify a case as certain were rather strict, a very small number of certain cases of RS was expected. However, we were surprised by the large number of cases classified as unlikely (43%) or excluded (31%). These results merit several comments concerning the definitions described above; the age of patients involved; the way RS was diagnosed by clinicians of our institution during the study period; and why the most astute clinician had, until recently, several reasons to overdiagnose RS.

One may allege that the criteria used to classify a case as probable RS were too strict, or that those rendering RS unlikely or excluded were too broad. We do not think this was the case, even though we do not have the pretention to propose them as the "gold standard" for diagnosis of RS. The necessity for every child with a possibility of RS to undergo biopsy was debatable in the 1970s and could still be so today. Nonetheless, in our hospital where 92% of the patients with presumptive cases of RS underwent biopsy or autopsy, we considered hepatic steatosis essential for a diagnosis of RS to be probable. Moreover, this large percentage of cases with histologic documentation, one of the highest ever reported in a series of RS (vs 30% to 40%^{6,23,24}), validates our conclusions.

The category "unlikely" was the most difficult to define. As already described, two or more of a list of eight characteristics were required. Even if several of these findings could have been considered sufficient by themselves to render a presumptive case unlikely, a more restrictive definition was preferred. The absence of a prodromal illness in children 12 months of age or more was one of these required findings. Indeed, in approximately 90% of the cases reported by the Centers for Disease Control, Atlanta, a prodromal illness occurred,²⁴ the absence of previous infection being more suggestive of metabolic disease rather than RS.²⁵ Bilirubin concentrations are characteristically normal or minimally elevated in RS.²⁰ Hyperammonemia has been observed in almost all patients early in the course of the illness,²⁰ except in grade I where ammonia levels are often normal.²⁶ Renal abnormalities are usually not severe in RS and typically consist of elevations in blood urea nitrogen concentrations; occasional cases of transient acute renal failure have been reported,^{27,28} but in some of these, central lobular necrosis was found on liver biopsy, rendering the diagnosis of RS doubtful.

Reye's syndrome may cause progressive cerebral herniation, with a rostro-caudal progression but no focal signs.²⁰ Even if the heart shows evidence of lipid accumulation, cardiac manifestations are extremely rare and have not been mentioned in recent reviews on RS.^{20,29} Signs of shock could be secondary to cerebral death or to hypovolemia, but are so unusual that they are omitted in descriptions of the clinical spectrum of the disease.^{20,29} Prolonged seizures can be associated with elevated cerebrospinal fluid protein levels because of a transient breakdown of the blood-brain barrier; in the majority of cases, however, cerebrospinal fluid protein levels remain below 0.5 g/L.³⁰ If present in a patient without seizures, elevated cerebrospinal fluid protein level would more likely suggest central nervous system infection.

Age distribution for our group of 49 patients (median age, 19 months) was similar to the original description of the disease by Reye et al¹ and to other series of sporadic cases of RS from Australia,⁵ Ireland,³¹ and England.³² Although

cases classified as excluded and unlikely RS were encountered in all age groups in our series (Fig 1), these patients were significantly younger compared with the total group of patients. This is not surprising considering that it may be particularly difficult in young children to differentiate RS from anoxic encephalopathy, inborn errors of metabolism, or other conditions.^{33,34}

Our study relates the experience of a large tertiary care pediatric hospital, staffed with a very active gastroenterology team, which has already proved its scientific interest in RS.³⁵ Over the years, this team has used the criteria proposed by the Centers for Disease Control, to diagnose RS. These criteria are very broad and nonrestrictive,^{3,18,24} which obviously allows overdiagnosis. Pathological confirmation is not required; an alteration in the level of consciousness with elevated transaminase or ammonia levels are enough to diagnose RS, even in comatose children. This is not specific enough to exclude clinically similar disorders.³⁶ These flaws in diagnostic criteria are so apparent that the Centers for Disease Control have recently drawn attention to the nonspecificity of the case definition and have suggested that it should be more rigorous.³⁴

During the 1970s, many publications from different sources emphasized the importance of recognizing RS early in children with acute alteration of consciousness. At the same time, the differential diagnosis of RS was rather limited, compared with what it is today. More recently, an extensive list of disorders mimicking RS have been described.^{11,12-16,37,38} Moreover, fatty metamorphosis of the liver was often used as an essential criterion for establishing a diagnosis of RS, until it was shown to be present in disorders of fatty acid oxidation and in defects of ureagenesis,^{16,39} and ubiquitous in children dying of a traumatic death or of a sudden unexpected natural death.⁴⁰

Because of all these considerations, the most astute and competent clinician had, until recently, many reasons to overdiagnose and overreport RS.

Broadening of the differential diagnosis of RS has not only served to establish an exhaustive list of RS mimickers but has rendered the clinician much more

circumspect today with a presumed case of RS. For clinicians, RS has become a diagnosis of exclusion. Obviously, acute encephalopathies misdiagnosed as RS in the past were not necessarily all genetic diseases or adenovirus type 7 infections. As reported by Hurwitz et al⁶ and in the present study, viral hepatitis, viral encephalitis, hypovolemic shock, etc. were often mistaken for RS. This happened because of different factors, such as fear among physicians of missing such a severe and treatable disease and their great and sometimes exaggerated enthusiasm toward this newly described entity. We agree entirely with Rowe et

al³⁶ that if inherited defects had been responsible for the majority of cases of RS in the past, the recent reduction in incidence would have to imply an implausibly large genetic shift in the population.

This change in the physician's perception of this disease coincides with the decreasing trend observed in the incidence of RS. A cause-effect relationship between both factors is hard to prove scientifically, since, by definition, a change of attitude is a subjective phenomenon. However, our results suggest that this possibility must be taken into account, as is the link between the decreasing trend of RS and aspirin use.

We have shown that the true incidence of RS has always been low in our institution since 1970. It is not possible, at this point, to generalize our data to other centers. However, our results indicate that the diagnostic criteria of RS should be reassessed by the Centers for Disease Control and that the apparent disappearance of RS must be reevaluated. Although it might appear to be a disturbing question, one must try to discover if this disappearance is a fact or a fancy.

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Neurologic Status and Intracranial Hemorrhage in Very-Low-Birth-Weight Preterm Infants

Outcome at 1 Year and 5 Years

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• Twenty-six very-low-birth-weight preterm infants with and without intracranial hemorrhage (ICH) were followed up prospectively from birth to school age to determine the relationship between ICH and subsequent neurologic and cognitive outcomes. All children had sequential cranial ultrasound examinations at birth and neurologic assessments at 3-month intervals during the first year, at 1 year of age, and at 5 to 6 years; psychometric assessments were done at 5 to 6 years. Seventeen children had no ICH, 3 had grade 1 ICH, 1 had grade 3 ICH, and 5 had grade 4 ICH. The 1-year Amiel-Tison neurologic assessment in 25 infants demonstrated that 14 were normal, 3 were suspect, and 8 were abnormal. By 5 to 6 years of age, 5 of 8 children neurologically abnormal at 1 year remained abnormal, 2 of 3 children neurologically suspect at 1 year remained suspect; while 9 of 15 children neurologically normal at 1 year remained normal,

the remaining 6 had become suspect. The predominant neurologic abnormality at 5 to 6 years was subtle neurologic dysfunctioning. The Wechsler Preschool and Primary Scale of Intelligence at 5 to 6 years revealed a mean group IQ score of 92.1. The Beery Visual Motor Integration Test results demonstrated that 18 of 26 children had mild to severe visual motor perceptual difficulties. Severe ICH (grades 3 and 4) correlated with abnormal neurologic performances at 1 and 5 to 6 years. Mild ICH (grade 1) and no ICH did not correlate with any one of the 1-year neurologic classifications. The 1-year status correlated with the 5- to 6-year neurologic outcome best for children who were either neurologically suspect or abnormal at age 1 year. The 1-year neurologic score did not correlate with 5- to 6-year IQ and Beery Visual Motor Integration Test scores.

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More recent studies of long-term outcomes in school-age children demonstrate that survivors of severe ICH remain abnormal.¹⁷ Some studies have reported that survivors of mild ICH may display a variety of subtle neurologic and cognitive dysfunction, including motor incoordination, hyperactivity, attention and learning deficits, and visual motor difficulties.^{18,17,18} However, more studies are needed to determine the exact extent of long-term sequelae associated with mild or asymptomatic ICH. Since 1980, the availability of cranial ultrasound has allowed accurate diagnosis of all grades of ICH, thus enabling physicians to correlate accurately ICH severity with outcome measures.

PURPOSE AND HYPOTHESIS

The purpose of this study was to determine and relate neurologic and cognitive outcomes in school-age children who had ICH with their 1-year neurologic results. The study objectives were to establish (1) whether an association exists between ICH severity and outcome at school age; (2) whether the 1-year neurologic status is an accurate predictor of school-age function; and (3) more specifically, whether transient and/or persistent neurologic abnormalities present during the first year are markers for later neurodevelopmental and cognitive disabilities.

We hypothesized that (1) severe ICH is associated with early and later childhood neurologic sequelae; (2) first-year neurologic status is a predictor of later neurologic functioning; and (3) transient and persistent neurologic abnormalities during the first postnatal year are indicators of later neurologic abnormalities.

Intracranial hemorrhage (ICH) is a common and clinically serious complication in the very-low-birth-weight preterm infant.^{1,2} The overall occurrence rate was reported to range between 40% and 60% from 1980 through 1985; after 1986, incidences were reported to be 13% to 48%.³⁻⁶ Intracranial hemorrhage is associated with an increased mortality rate and risk for serious neu-

rologic sequelae.¹ The incidence of major neurologic sequelae increases with the severity of hemorrhage and can be associated with posthemorrhagic complications.^{1,4,6,7} Long-term neurologic morbidity observed in some survivors includes hydrocephalus, motor handicaps, and mental retardation,^{8,9} as well as learning and developmental disabilities.^{6,7,10-13}

Initial follow-up studies, which primarily focused on infancy and early childhood outcomes, demonstrated that severe ICH (grades 3 and 4) was associated with significant mental or motor handicaps.^{8,9,14-16} Mild ICH (grades 1 and 2) was often related to transient or subtle neurologic abnormalities present during the first postnatal year, which frequently normalized by the end of the first year of life.^{8,9}

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PATIENTS AND METHODS

Patients

Birth to 1 Year.—The study population was derived from an original sample of 64 appropriate-for-gestational-age, very-low-birth-weight (≤ 1500 g), preterm infants studied from August 1979 to December 1980.¹⁹ All were outborn and transferred to Cincinnati (Ohio) Children's Hospital Medical Center Regional Newborn Intensive Care Unit. These infants had the following characteristics: mean birth weight of 1113 g (range, 580 to 1480 g), mean gestational age of 29 weeks (range, 24 to 33 weeks), and mean Apgar scores of 4 at 1 minute and 6 at 5 minutes; there were 33 boys and 31 girls, 10 black and 54 white. The rate of ICH was 54.7% (35/64). The neonatal mortality rate was 46.9% (30/64), leaving 34 infants for potential follow-up study. Among the 30 neonatal deaths, 23 (76.7%) occurred in children with ICH.

Initially, the 34 surviving infants were followed up from birth to 1 year. Their characteristics were not different from the original group of 64 infants, except for a significant difference in sex distribution: 24 were girls and 10 were boys ($P < .05$).

Follow-up at 5 to 6 Years.—At the age of 5 to 6 years, 26 of 34 infants could be located for follow-up assessment. Eight children had been unavailable for follow-up for the following reasons: two had moved more than 320 km from our institution, one family refused follow-up, and five children could not be located. The characteristics of the 26 children were not different from the total sample of 64 infants enrolled at birth or from the group of 34 infants followed up during the first year.

Measures

Birth to 1 Year.—Cranial ultrasonography was performed sequentially on days 1, 4, 7, 13, 21, and 28 of life to document presence or absence of ICH¹⁹; ultrasounds were not evaluated for other lesions. Grades of ICH included 1, subependymal hemorrhage; 2, intraventricular hemorrhage without ventricular distention; 3, intraventricular hemorrhage with ventricular distention; and 4, intraventricular hemorrhage with cerebral parenchymal hemorrhagic involvement.⁴ Patients with periventricular leukodensities were categorized as having grade 4 ICH.

Neurodevelopmental assessments were done at 3, 6, 9, and 12 months' postconceptional age using the Amiel-Tison Neurologic Assessment.²⁰ At the end of the first year, infants were assigned a neurologic score by one of us (J.S.), "blinded," ie, unaware of the initial intraventricular hemorrhage grade. Neurologic classification was as follows: (1) normal, no neurologic abnormalities; (2) suspect, transient neurologic abnormalities that disappeared by the end of the first year; or (3)

abnormal, persistent neurologic abnormalities throughout and at the end of the first year of life. Abnormal neurologic signs included persistent abnormalities of tone (hypertonicity or hypotonicity), abnormal persistence of primitive reflexes, abnormal eye movements, abnormal levels of arousal and consciousness, and poor head control.

Five to 6 Years.—The 5- to 6-year follow-up assessment consisted of neurologic and psychometric evaluations, performed by examiners different from those involved in the study phase from birth to 1 year. To reduce investigator bias, examiners were blinded, ie, not aware of each child's ICH grade, nursery course, and 1-year neurologic score.

A standard neurologic evaluation was performed by one of us, a pediatric neurologist (L.M.F.), as described by Baird and Gordon.²¹ Three neurologic classifications were used: (1) normal, no neurologic abnormalities; (2) suspect, fine- or gross-motor deficit, attention-deficit disorders, or language inefficiency; and (3) abnormal, static neuromotor deficits, including hemiparesis, quadriplegia, spastic diplegia, blindness, deafness, seizure disorder, or hydrocephalus.

Impairment of fine-motor, gross-motor, or both skills included difficulty with mirror or fine-finger movements, hop and balance on one foot or both feet, or mild hemiatrophies.

Psychometric evaluations measured cognitive functioning using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) and visual motor perceptual status using the Beery Visual Motor Integration Test (VMI).²² The WPPSI has a full scale and two subscales—verbal and performance. Based on the full-scale scores, three categories were defined as follows: normal, IQ of 85 or higher; borderline, IQ of 71 to 84; and abnormal, IQ of 70 or lower.

The Beery VMI is a form-copying test of 24 geometric forms. Based on raw scores of 0 to 24, age-equivalent percentiles and standard scores were assigned. Standard scores have a mean of 10 and an SD of 3. Children with standard scores of 7 or more had normal age-related visual motor skills, while those with scores of 7 or less had abnormal skills.

Data Analysis

Descriptive statistics and correlation coefficients among variables were obtained. Multivariate regression analysis was performed to examine the combined effect of ICH and other predictors on outcome.

RESULTS

Birth ICH and 1-Year Outcome

The distribution of ICH for the 26 survivors studied was as follows: 17 had no ICH; 3 had grade 1; 1 had grade 3; and 5 had grade 4.

Nineteen children developed transient or persistent ventricular dilatation during the first year; these included 10 children with no ICH and all 9 children with any degree of ICH. Only 7 children, all with no ICH, had no ventriculomegaly. Posthemorrhagic hydrocephalus requiring a ventriculoperitoneal shunt developed in one child with grade 4 ICH.

Twenty-five of 26 children were examined during and at the end of the first year with the Amiel-Tison Neurologic Assessment: 14 were normal, 3 were suspect (ie, demonstrating transient neurologic abnormalities at some point during the first year that had disappeared by the end of the first year), and 8 were abnormal (showing persistent neurologic abnormalities throughout and at the end of the first year). One child who was unavailable for follow-up testing was reported by a community health clinic to have normal neurodevelopmental status during and at the end of the first year.

The ICH grade correlated negatively with a normal 1-year neurologic outcome ($r = -.58$; $P < .001$). The more severe the ICH injury was, the less normal the neurologic performance. As shown in Table 1, five of six infants with grades 3 and 4 ICH were classified as having persistent neurologic abnormalities at the age of 1 year; one child with grade 4 ICH was neurologically normal at 1 year. By contrast, among 20 children with no or mild ICH (grade 0 and 1), 14 were neurologically normal at 1 year, whereas 6 had transient persistent neurologic sequelae.

Birth ICH and 5- to 6-Year Outcome

Neurologic evaluation at 5 to 6 years showed 9 children were normal, 11 were suspect, and 6 were abnormal. The predominant neurologic dysfunctions were subtle motor disabilities consisting of fine-motor or gross-motor incoordination or both. Specific neurologic abnormalities among children with no ICH or grade 1 ICH included sensorineural hearing loss, seizures, and spastic diplegia, whereas children with grades 3 and 4 ICH demonstrated hemiplegia, diplegia, quadriplegia, blindness, and deafness.

The 5- to 6-year psychometric assessments revealed a WPPSI mean full-

scale summary score of 92.1 for all groups combined. Scores were in the normal range in 19 children, borderline in 6 children, and abnormal in only 1 child. The VMI mean standard score was 4.19. The majority of children, 18 of 26, demonstrated dysfunctions on VMI testing; only 8 children had normal visual-motor skills. Furthermore, 21 children demonstrated a variety of additional deficits on psychometric testing; these deficits included speech, hearing, language, and attention problems. In these subjects, future follow-up psychological evaluations were recommended in one or more of these specific areas for adequate school placement.

Severity of ICH did not correlate with 5- to 6-year cognitive functioning on the WPPSI scale ($r = -.17$; not significant [NS]) (Table 2). Among children with grade 4 ICH, two of five had normal full-scale scores; indeed, one of these two children had an exceptional IQ of 127. Among six children with borderline IQ scores, however, three had no ICH.

Similarly, ICH did not correlate with 5-year VMI scores ($r = -.10$; NS). Despite ICH status, 18 children had visual motor perceptual difficulties.

Severity of ICH correlated negatively with 5- to 6-year neurologic outcome ($r = -.41$; $P < .01$). As shown in Table 1, four of six children with severe ICH (grades 3 and 4) were neurologically abnormal at 5 years, one was suspect, and one was normal; whereas among 20 children with no or minimal ICH (grades 0 and 1), 8 were neurologically normal, 10 demonstrated subtle neurologic dysfunction, and only 2 were abnormal.

Relationship Between First-Year and 5- to 6-Year Neurologic Outcomes

The first-year Amiel-Tison Neurologic Assessment score correlated significantly with the 5- to 6-year neurologic assessment ($r = .53$; $P < .01$) (Table 3). Among 11 children who were either abnormal or suspect at 1 year of age, 9 remained suspect or abnormal at 5 to 6 years of age. The remaining 2 of 11 children showed improvement and were neurologically normal at 5 to 6 years. Of 15 children normal at 1 year of age, 9 remained normal, while 6 were now suspect, demonstrating a combination of fine- and gross-motor dysfunction; none was abnormal.

Table 1.—Intracranial Hemorrhage (ICH) Status and 1-Year and 5- to 6-Year Neurologic Outcome							
ICH Grade	Normal		Suspect		Abnormal		n
	At 1 y	At 5-6 y	At 1 y	At 5-6 y	At 1 y	At 5-6 y	
No ICH	12 (+1)*	7	2	8	2	2	17
1	1	1	1	2	1	0	3
2	0	0	0	0	0	0	0
3	0	0	0	0	1	1	1
4	1	1	0	1	4	3	5
Total	15	9	3	11	8	6	26

*One child was not examined by investigator during the first year. Records from a community health clinic reported normal neurologic status during the first year.

Table 2.—Intracranial Hemorrhage (ICH) Status and Psychometric Scores				
ICH Grade	Verbal IQ	Performance IQ	Full-Scale WPPSI* IQ	VMI Standard Score* IQ
0 (n=17)	≥85 (n=13) 70-80 (n=4)	≥85 (n=13) 70-84 (n=4)	≥85 (n=14) 70-84 (n=3)	≥7 (n=5) <7 (n=12)
1 (n=3)	≥85 (n=3)	≥85 (n=3)	≥85 (n=3)	≥7 (n=2) <7 (n=1)
3 (n=1)	≥85 (n=1)	70-84 (n=1)	70-85 (n=1)	≥7 (n=1)
4 (n=5)	≥85 (n=2) 70-84 (n=2) <70 (n=1)	≥85 (n=2) 70-84 (n=1) <70 (n=1)	≥85 (n=2) 70-84 (n=1) <70 (n=1)	≥7 (n=1) <7 (n=4)

*WPPSI indicates Wechsler Preschool and Primary Scale of Intelligence; VMI, Beery Visual Motor Integration Test.

Table 3.—Relationship of 1-Year and 5- to 6-Year Neurologic Status				
	At 5 to 6 y			Total
	Normal	Suspect	Abnormal	
At 1 y				
Normal	9	6	0	15
Suspect	0	2	1	3
Abnormal	2	1	5	8
Total	11	9	6	26

Five- to 6-year cognitive functioning did not correlate with the 1-year neurologic status. Most children, regardless of their 1-year neurologic status, had normal full-scale IQs at 5 to 6 years. One child with grade 4 ICH and an abnormal 1-year neurologic status had an exceptional 5- to 6-year IQ of 127.

Significant relationships existed between 5- to 6-year neurologic status and WPPSI ($r = .39$; $P < .05$), as well as VMI ($r = .66$; $P < .001$). Thus, at 5 to 6 years, there was a correlation between neurologic and cognitive status.

Multivariate Approach to Predicting 1- and 5- to 6-Year Outcomes in Infants With ICH

Regression Analysis: 1-Year Neurologic Outcome.—One-year neurologic scores in the follow-up sample were predicted by the following variables in descending order of importance: ICH (standardized β [SB] = .52), gestational age (SB = .42), and sex (SB = -.42); birth weight did not add to the prediction (SB = -.06). The amount of variance in the 1-year neurologic performance accounted for by these four

predictors was .57 (multiple r [MR] = -.75).

These results show that ICH is the most relevant factor in the prediction of the 1-year neurologic outcome (25% of the variance) followed by gestational age and sex (32% of the variance).

Regression Analysis: 5- to 6-Year Neurologic Outcome.—The 5- to 6-year neurologic outcome was predicted by the following variables: ICH (SB = .35), gestational age (SB = -.37), birth weight (SB = .06), sex (SB = -.01), and 1-year neurologic performance (SB = .36). The amount of variance accounted for by these variables in the 5- to 6-year neurologic performance was 33% (MR = .57). As expected, the short-range predictor of 1-year neurologic outcomes makes the highest contribution, yet neonatal ICH is not a negligible predictor. Although important, the relative contribution of ICH and gestational age diminished, while that of 1-year neurologic outcome increased.

Similarly, predictions regarding 5- to 6-year WPPSI performance (amount of variance accounted for 13%, MR = .36) and VMI performance (amount of variance accounted for 10%, MR = .32) were low. The importance of ICH as a predictor was reduced (SB = .04).

By contrast, the predictability of the 5- to 6-year neurologic performance was enhanced by considering as predictors the WPPSI (SB = -.16) and VMI (SB = -.30), and the amount of variance increased to 42% (MR = .65).

COMMENT

In this study, ICH severity correlated with the extent of neurologic sequelae seen at early (1-year) and school-age (5- to 6-year) follow-up evaluations. The more severe the ICH, the less normal were neurologic performances. Children with severe ICH (grades 3 and 4) were classified as neurologically suspect or abnormal on early and later neurologic examinations. Mild ICH (grade 1) was associated with all neurologic classifications at 1 year, whereas it was primarily associated with subtle neurologic dysfunctioning (suspect neurologic category) at 5 to 6 years. Thus, ICH is an important variable that influences early and later neurologic outcomes in affected infants.

Our results associating ICH and neurologic outcomes are consistent with previous longitudinal studies of short- and long-term outcomes. In contrast to Palmer et al,²³ we did not find an association between ventriculomegaly and outcome measures. Furthermore, in our study, ICH severity appeared to be an important factor in the development of posthemorrhagic ventricular dilatation, since all children with ICH had persistent ventriculomegaly throughout the first year of life.

The ICH grading system used in 1980 made no distinction between two types of grade 4 ICH lesions, cerebral parenchymal hemorrhage and periventricular leukomalacia. Thus, outcomes were not differentiated between these two lesions. This is an important issue because of controversial aspects pertaining to grade 4 ICH, ie, hemorrhage vs ischemia, their associated pathophysiologic risk factors, and prognostic outcomes. One attractive hypothesis suggests that intracerebral hemorrhage is only a component of a larger lesion, ischemic in nature.²⁴

The absence of ICH did not guarantee a normal neurologic score either at 1 year or 5 to 6 years. Although most children with no ICH were normal on early follow-up evaluation, they primarily demonstrated subtle neuromotor dysfunction at school age. Thus, while ICH is a major factor influencing future neurologic outcome, additional variables also have influence. We postulate that such variables include severity of perinatal medical complications, birth growth parameters (birth weight), and maturation (gestational age). Furthermore, since the correlation between ICH and neurologic status diminishes somewhat with increasing age, postnatal socioeconomic environment is also likely an important variable influencing neurologic outcome. Previous studies have substantiated the importance of such variables on neurologic outcome.¹⁷

Overall, our results indicate that all very-low-birth-weight preterm infants with and without ICH should be monitored throughout early childhood for neurologic sequelae to detect subtle and overt abnormalities requiring special attention.

The 1-year neurologic outcome was the most accurate predictor of the 5- to

6-year neurologic outcomes vs other predictors, including ICH status, birth weight, gestational age, and sex. When specific 1-year neurologic classifications were compared with 5- to 6-year classifications, our findings were slightly different from previous studies. These reports concluded that the best correlations between infancy and school-age neurologic outcomes were for children who were either normal or abnormal on early examinations.^{3,18,25} We found the greatest correlation for children who were either neurologically suspect or abnormal during the first year. Most infants with transient or persistent neurologic abnormalities during the first year continued to display subtle or overt neurologic deficits at age 5 to 6 years. Thus, transient and persistent neurologic abnormalities during the first year of life seem to be important precursors of persistent neurologic deficits.

The 1-year neurologic score was not an accurate indicator of 5- to 6-year functioning for infants neurologically normal at 1 year of age. At 5 to 6 years there were fewer neurologically normal children. Therefore, a normal 1-year neurologic score did not preclude neurologic dysfunctioning at the age of 5 to 6 years.

Thus, for the 1-year neurologic examination, the sensitivity is better than the specificity; in other words, the chance of detecting abnormal children at 5 to 6 years of age is better than that of identifying healthy survivors. These results should satisfy the goals of the clinician.

The differences between our results and those of previous studies regarding correlations between early and later neurologic outcomes may reflect different study methods. Some previous studies included only infants with "symptomatic" ICH,^{18,25} while others did not account for the presence of ICH at all.³ Furthermore, results of our study may be limited by a small sample size and poor follow-up rate.

In contrast to neurologic outcomes, 5- to 6-year cognitive outcomes did not correlate with either ICH severity or 1-year neurologic outcome. The majority of children had normal IQ scores and abnormal VMI scores despite ICH or 1-year neurologic status. Thus, while most children demonstrated normal

overall cognitive function, they displayed subtle dysfunction in the form of abnormal VMI abilities and other learning disabilities.

The 5- to 6-year neurologic and cognitive sequelae in very-low-birth-weight preterm infants with and without ICH are primarily subtle motor and perceptual dysfunctions. Intracranial hemor-

rhage has significant influence on neurologic outcomes since ICH severity correlated with the extent of neurologic sequelae. Although the school-age abnormalities described are characterized as subtle, they may presage important future problems of learning disability and school failure, making early identification and intervention imperative.

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In Other AMA Journals

ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

Childhood Ki-1 Lymphoma: A Report of Two Cases

Kiniyuki Oka, MD; Naoyoshi Mori, MD; Mizu Kojima, MD; Tatsuo Iijima, MD; Takashi Hanada, MD; Masahiro Tsuchida, MD (*Arch Pathol Lab Med*. 1989;113:998-1002)

Juvenile Xanthogranuloma: Clinical and Pathologic Characterization

Steven R. Tahan, MD; Cecile Pastel-Levy, MD; Atul K. Bhan, MD; Martin C. Mihm, Jr, MD (*Arch Pathol Lab Med*. 1989;113:1057-1061)

Hypophosphatemia in Breast-fed Low-Birth-Weight Infants Following Initial Hospital Discharge

Robert T. Hall, MD; Robin E. Wheeler, MS, RD; Michael B. Montalto, MS; John D. Benson, PhD

• The present study evaluated 12 infants with birth weights less than 2000 g who received human milk plus a multivitamin supplement and 20 similar infants who received standard cow's milk formula for 16 weeks from the time of initial hospital discharge. Examination at birth, at hospital discharge (study entry), at 4 and 16 weeks after hospitalization, and at 52 weeks of age revealed no intergroup differences in body weight, length, and head circumference. Hypophosphatemia (plasma phosphorus concentration ≤ 1.45 mmol/L) developed in 6 infants fed human milk (5 infants at 4 weeks and 1 infant at 16 weeks of study). Mean vitamin D intakes, but not calcium and phosphorus intakes, were significantly lower during hospitalization in human milk-fed infants with hypophosphatemia (44 [25, SD] IU/d) compared with those without hypophosphatemia (322 [180] IU/d). These data indicate that human milk-fed, low-birth-weight infants are at risk for hypophosphatemia following initial hospital discharge. Plasma calcium, phosphorus, and alkaline phosphatase concentrations at hospital discharge may not predict the infants at risk. Vitamin D supplementation early in the infants' hospital course may prevent hypophosphatemia. (AJDC. 1989;143:1191-1195)

One hypomineralization is a significant problem in low-birth-weight infants exclusively fed human milk.¹⁻⁶ There are adequate data indicating that hypophosphatemia and rickets during the initial hospital course^{1,6} can be prevented in these infants by giving calci-

um, phosphorus, and vitamin D supplements.⁷⁻¹²

However, low-birth-weight infants have been studied infrequently beyond hospitalization.¹³⁻¹⁶ The purpose of the present study was to evaluate biochemical evidence of bone hypomineralization⁸ in human milk-fed low-birth-weight infants compared with formula-fed infants after hospital discharge.

PATIENTS AND METHODS

Infants were eligible for participation in the study if their birth weights were below 2000 g and there were no major congenital malformations, necrotizing enterocolitis, bronchopulmonary dysplasia, malabsorption, or other apparent conditions affecting the nutritional status. Parents were approached regarding their infant's participation, and informed written consent was obtained before entry in the study, which was approved by the Institutional Review Board. No attempt was made to assign infants to the human milk-fed vs formula-fed group. The study was initiated during the week before discharge from the hospital. Management prior to that time was at the discretion of the attending physician. However, calcium, phosphorus, vitamin D, and energy intake measurements were obtained for all infants during initial hospitalization. Mean daily intakes of calcium and phosphorus were derived from human milk composition data of Lemons et al.¹⁶

The human milk-fed group was given 1 mL/d of a multivitamin preparation (Vi-Daylin, Ross Laboratories, Columbus, Ohio) containing 400 IU of vitamin D at hospital discharge. Any previous mineral supplementation was discontinued at study entry. Infants with birth weights below 1500 g generally received supplementation during initial hospitalization with calcium, phosphorus, and vitamin D in the form of powdered human milk fortifier or premature infant formula in accordance with recommendations of the attending physician. Additional supplementation with vitamin D from multivitamin preparations was also given in accordance with recommendations of the attending phy-

sician. No formula supplementation was given to human milk-fed infants during the 16 weeks following hospital discharge.

Formula-fed infants were given a 2800-kJ/L cow's milk formula (Similac With Iron, Ross Laboratories) at study entry during the week prior to hospital discharge. Vitamin supplementation was given to the formula-fed group during hospitalization at the discretion of the attending physician. Infants with a birth weight below 1500 g were generally given a whey-predominant premature infant formula containing 3400 kJ/L that was switched to the 2800-kJ/L formula at study entry. No vitamin supplementation was given following study entry in addition to that present in the formula.

Plasma calcium, phosphorus, and alkaline phosphatase measurements were obtained at study entry and at 4 and 16 weeks following study entry. Body weight, length, and head circumference were obtained by one of us (R.E.W.) at study entry and at 2, 4, 8, 12, and 16 weeks following study entry. From 16 weeks after study entry until 52 weeks of age, infants were not given a prescribed feeding protocol. At 1 year of age, anthropometric measures were made. All weight measurements after study entry were obtained on the same scale calibrated to a 10-g accuracy. Length was obtained with the infant supine on a length board using two attendants. Head circumference measurements were obtained with the same tape measure throughout the study.

Statistical evaluations of differences between groups were made using the Student *t* test for mean values and the Fisher Exact Test for frequencies. A stepwise discriminant analysis was performed using a BMDP 7M program to evaluate differences between infants with and without hypophosphatemia.¹⁷ A plasma phosphorus concentration of 1.45 mmol/L or lower and an alkaline phosphatase concentration of 450 IU/L or greater were considered significantly abnormal.^{3,18,19}

RESULTS

Descriptive data from the infants fed human milk and formula are shown in

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Reprints not available.

Table 1. The only significant intergroup difference was race; there were significantly more white infants in the human milk group ($P < .001$).

Groups did not differ in growth or absolute weight, length, and head circumference during the first 4 months of the study or at 1 year of age (Table 2).

Mean plasma concentrations of calcium, phosphorus, and alkaline phosphatase were within normal limits and did not differ between the two groups at study entry (Table 3). No infant had a phosphorus concentration of 1.45 mmol/L or lower (hypophosphatemia) or an alkaline phosphatase concentration of 450 IU/L or greater (hyperphosphatasia) at study entry. However, the mean plasma phosphorus concentration was significantly lower and the mean alkaline phosphatase concentration significantly higher in the group fed human

milk by 4 weeks after study entry. These differences persisted at study week 16. No formula-fed infant experienced hypophosphatemia or hyperphosphatasia during the study period.

Stepwise discriminant analysis was performed using 12 variables to distinguish etiologic factors for hypophosphatemia: (1) race, (2) sex, (3) birth weight, (4) length, (5) gestational age, (6) mean vitamin D intake per day, (7) mean calcium intake in kilograms per day, (8) mean phosphorus intake in kilograms per day, (9) mean energy intake in kilograms per day, (10) type of feeding, (11) mean Apgar scores at 1 and 5 minutes of age, and (12) mean weight at 16 weeks. This procedure correctly classified 93.5% of infants using two variables, ie, type of feeding and vitamin D intake. All infants with hypophosphatemia received human milk and had a significant-

ly lower vitamin D intake during hospitalization (mean [SD], 44 [25] IU/d) than infants without hypophosphatemia (322 [180] IU/d, Table 4). This difference was due to low vitamin D intake early in the hospital course of six human milk-fed infants in whom hypophosphatemia developed. Although there was a difference in calcium and phosphorus intake between infants fed formula and human milk, there was not a difference in these mineral intakes in human milk-fed infants with and without hypophosphatemia. Energy intakes were nearly identical among all infants.

Additional evaluation of infants with and without hypophosphatemia appears in Table 5. Mean birth weights of the two groups were 1715 g (infants with hypophosphatemia) and 1611 g (infants without hypophosphatemia; P , not significant). Gestational age and age at study entry were not different. There was likewise no difference in the sex, race, severity of illness, or length of hospital stay between the two groups of human milk-fed infants.

Five of 12 infants had hypophosphatemia at study week 4. A sixth infant had a plasma phosphorus concentration of 1.25 mmol/L at 16 weeks. One infant had hyperphosphatasia at 4 weeks and 2 infants had it at 16 weeks. Three infants required supplementation with calcium and phosphorus because of persistent hypophosphatemia at 16 weeks. One additional infant in the human milk-fed group (patient 13), whose birth weight was 505 g, was dropped from the study at 4 weeks because she had a plasma phosphorus concentration of 1.15 mmol/L and an alkaline phosphatase

Table 1.—Descriptive Data in Two Nutrition Groups*

	Human Milk (n=12)	Formula (n=20)
Mean birth weight, g	1663 (235)	1503 (340)
Mean birth length, cm	43.2 (3.3)	41.6 (3.7)
Mean birth head circumference, cm	29.3 (1.6)	28.6 (2.4)
Mean gestational age, wk	33.0 (1.5)	31.6 (2.4)
Intrauterine growth, appropriate for gestational age/small for gestational age, No. of infants	10/2	18/2
Mean Apgar score		
1-min	6.4 (1.8)	6.9 (1.9)
5-min	8.3 (0.9)	7.8 (1.4)
Sex, M/F, No. of infants	3/9	10/10
Race, W/B, No. of infants†	11/1	13/7
Mean age at study entry, d	25 (10)	36 (20)

*Values in parentheses are SDs.

† $P < .001$.

Table 2.—Mean Growth Measurements in Human Milk and Formula Groups

Growth Measurement	Study Entry		4 wk		8 wk		12 wk		16 wk		1 y	
	Human Milk	Formula	Human Milk	Formula	Human Milk	Formula	Human Milk	Formula	Human Milk	Formula	Human Milk	Formula
Age, d	25	36	53	64	81	92	108	120	137	147	390	363
Weight, g	2000	2025	2878	3006	3970	3931	4689	4764	5348	5350	8879	8245
Weight gain, g/d	36	35	39	33	26	31	23	21	14	14
Weight gain, g/kg per day	13	12	10	8	6	7	4	4	2	2
Length, cm	44	44	47	48	51	51	54	54	56	56	72	71
Length gain, mm/d	1.47	1.46	1.24	1.22	1.05	1.13	0.79	0.80	0.63	0.63
Head circumference, cm	32	32	35	35	37	38	39	39	40	41	46	46
Head circumference gain, mm/d	1.10	1.00	0.86	0.83	0.54	0.61	0.49	0.47	0.24	0.24

Table 3.—Concentrations of Calcium, Phosphorus, and Alkaline Phosphatase in Human Milk and Formula Groups*

	Study Entry		4 wk		16 wk	
	Human Milk	Formula	Human Milk	Formula	Human Milk	Formula
Calcium, mmol/L	2.50 (0.05)	2.45 (0.05)	2.45 (0.05)	2.45 (0.10)	2.55 (0.10)	2.55 (0.05)
Phosphorus, mmol/L	1.85 (0.15)	2.10 (0.20)	1.50 (0.25)†	2.15 (0.15)	1.70 (0.30)†	2.00 (0.15)
Alkaline phosphatase, IU/L	236 (95)	187 (53)	380 (155)†	182 (66)	241 (90)†	169 (37)

*All values are mean (SD).

† $P < .001$.

Table 4.—Mean Intakes During Hospitalization*

Group	Patient No.	Energy Intake, kJ/kg per Day	Calcium Intake, mg/kg per Day	Phosphorus Intake, mg/kg per Day	Vitamin D Intake, mg/kg per Day
Formula	1	378	91	53	311
	2	416	109	56	404
	3	403	106	56	465
	4	399	147	96	240
	5	420	98	58	458
	6	391	67	45	88
	7	336	57	39	77
	8	374	94	70	385
	9	462	72	54	141
	10	344	50	59	308
	11	403	105	83	114
	12	244	167	99	239
	13	466	125	65	690
	14	445	71	47	105
	15	416	107	54	388
	16	403	106	56	398
	17	454	93	64	444
	18	391	86	70	517
	19	416	99	54	428
	20	370	67	51	101
	Mean (SD)	395 (50)	96 (29)	61 (16)	315 (172)
Human milk with hypophosphatemia	1	424	50	28	31
	2	424	83	42	12
	3	370	48	29	35
	4	412	80	47	70
	5	344	40	35	79
	6	365	48	22	40
	Mean (SD)	391 (34)	58 (18)	34 (9)	45 (25)
Without hypophosphatemia	1	416	76	47	363
	2	407	98	57	537
	3	365	39	18	642
	4	420	94	51	126
	5	378	54	33	363
	6	412	60	30	59
	Mean (SD)	399 (21)	70 (23)	39 (15)	322 (180)

*For the formula group compared with the human milk group with hypophosphatemia, P was not significant for energy intake, $P = .006$ for calcium intake, $P = .0004$ for phosphorus intake, and $P = .0001$ for vitamin D intake; for the formula group compared with the human milk group without hypophosphatemia, P was not significant for energy intake and vitamin D intake, $P = .058$ for calcium intake, and $P = .005$ for phosphorus intake; and for the human milk group with hypophosphatemia compared with the human milk group without hypophosphatemia, P was not significant for energy intake, calcium intake, and phosphorus intake and $P = .0008$ for vitamin D intake.

concentration of 910 IU/L; she was given supplementation with calcium and phosphorus.

Linear growth by SD from normal median values²⁰ in the infants with and without hypophosphatemia is presented in Table 6. There were no significant differences, although the infants with hypophosphatemia always had a slightly greater length percentile and incremental growth compared with infants without hypophosphatemia.

COMMENT

Data from the present study indicate that hypophosphatemia and hyperphosphatemia, which are plasma markers for bone hypomineralization and rickets, occur in a large percentage of low-birth-weight infants following hospitalization in spite of normal values at discharge. In

the present study, these infants were confined to those who were fed human milk but failed to receive adequate vitamin D supplementation. This finding was unexpected, since infants were receiving supplemental calcium, phosphorus, and vitamin D with human milk fortifier or premature formula during hospitalization. However, the powdered fortifier provided only 260 IU of vitamin D per 100 mL of fortified breast milk (1 package contains 25 mL), and the liquid fortifier provided only 61 IU of vitamin D per 100 mL when added to an equal volume of breast milk. Calculation of vitamin D intakes from hospital records revealed that all six infants with hypophosphatemia had prolonged periods of minimal vitamin D intake early in their hospital course. This was due to the perception that the multivitamin

preparations commonly used either were causing gastric residuals and abdominal distention or were associated with an increased risk of necrotizing enterocolitis from hyperosmolality.²¹

It is of interest that hypophosphatemia developed in human milk-fed infants with a low vitamin D intake who received calcium and phosphorus supplements in quantities similar to infants with higher vitamin D supplementation in whom hypophosphatemia did not develop. Four of six infants who experienced hypophosphatemia had a birth weight between 1500 and 2000 g. Previous reports have generally emphasized very-low-birth-weight infants (<1500 g) as the population at risk.

Linear growth in human milk-fed infants, including those who experienced hypophosphatemia, was not different from that in formula-fed infants during the 16-week study period and was within normal limits at 1 year of age. Greer et al²² reported decreased body length at 1 year of age in solely breast-fed term infants without vitamin D supplementation. However, three infants in our group with hypophosphatemia that persisted to 16 weeks did receive calcium and phosphorus supplements until their hypophosphatemia resolved.

The present data indicate that biochemical markers of bone mineralization obtained at the time of hospital discharge may not predict the preterm infant at risk for hypophosphatemia. The data emphasize the importance of vitamin D supplementation, particularly in low-birth-weight infants fed human milk. Concentrations of vitamin D present in human milk fortifiers do not meet the needs of low-birth-weight infants. A large dose of intramuscular vitamin D given early in the hospital course might have prevented hypophosphatemia in the infants who did not receive adequate supplementation.

Additional factors in the development of hypophosphatemia may be variability in the concentrations of calcium and

Table 5.—Human Milk-Fed Infants

Patient No.	Birth Weight, g	Gestational Age, wk	Age at Study Entry, d	Lowest Phosphorus Concentration, mmol/L (Study Week)	Highest Alkaline Phosphatase Concentration, IU/L (Study Week)
Mean Plasma Phosphorus Concentration ≤ 1.45 mmol/L					
1	1760	32	17	1.30 (4)	303 (4)
2*	1408	30	39	1.25 (4)	682 (4)
3	1910	34	14	1.45 (4)	271 (4)
4*	1330	32	35	1.05 (4)	294 (4)
5	1940	35	16	1.25 (16)	374 (4)
6*	1941	34	26	1.25 (4)	359 (4)
Mean	1715	33	25	1.25†	381
Mean Plasma Phosphorus Concentration > 1.45 mmol/L					
1	1440	34	28	1.60 (16)	574 (4)
2	1446	31	42	1.50 (16)	310 (16)
3	1700	33	21	1.75 (0)	133 (16)
4	1810	34	24	1.75 (4)	231 (0)
5	1840	34	14	1.60 (16)	260 (4)
6	1430	33	20	1.60 (4)	563 (4)
Mean	1611	33	25	1.65	345

*These patients received calcium and phosphorus supplementation at 16 weeks for persistent hypophosphatemia.

† $P < .01$.

Table 6.—Linear Growth in Infants With and Without Hypophosphatemia Relative to Normal Median Values of Healthy Term Infants*

	Linear Growth Compared With Normal Median Values						
	Study Entry	2 wk	4 wk	8 wk	12 wk	16 wk	1 y
Hypophosphatemia	-3.04 (0.06)	-3.89 (0.03)	-3.53 (0.14)	-2.87 (0.36)	-2.68 (0.91)	-2.63 (1.04)	0.67
No hypophosphatemia	-3.97 (0.02)	-4.03 (0.01)	-3.80 (0.03)	-3.40 (0.08)	-3.25 (0.12)	-3.11 (0.29)	-1.81

*All values are mean (SD).

phosphorus in human milk and inconsistent intake of vitamin D supplementation following discharge. These variables were not evaluated in the present study. Continued vigilance is necessary to ensure adequate calcium, phosphorus, and vitamin D intakes in low-birth-weight infants during and after hospitalization.

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ARCHIVES OF GENERAL PSYCHIATRY

Depressive Disorders in Childhood: IV. A Longitudinal Study of Comorbidity With and Risk for Anxiety Disorders

Maria Kovacs, PhD; Constantine Gatsonis, PhD; Stana L. Paulauskas, PhD; Cheryl Richards (*Arch Gen Psychiatry*. 1989;46:776-782)

Cortisol Secretion in Prepubertal Children With Major Depressive Disorder

Joaquin Puig-Antich, MD; Ronald Dahl, MD; Neal Ryan, MD; Hana Novacenko, MS; Deborah Goetz, PhD; Janet Twomey; Timothy Klepepr (*Arch Gen Psychiatry*. 1989;46:801-809)

Nasal Intermittent Positive-Pressure Ventilation Offers No Advantages Over Nasal Continuous Positive Airway Pressure in Apnea of Prematurity

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Neil N. Finer, MD, FRCP(C); Katherine L. Peters, RN, BScN, MN

• A prospective, randomized, crossover trial was performed to compare the efficacy of nasal intermittent positive-pressure ventilation with nasal continuous positive airway pressure in infants of less than 32 weeks of gestation. Continuous positive airway pressure was delivered at end-expiratory pressures of 4 cm H₂O, while peak pressures of 20 cm H₂O and end-expiratory pressures of 4 cm H₂O were used during nasal intermittent positive-pressure ventilation at ventilatory rates of 20 breaths per minute. The frequency and extent of apnea and bradycardia during a 6-hour period in a patient receiving nasal continuous positive airway pressure were compared with a similar crossover period of nasal intermittent positive-pressure ventilation. Although the infants had slightly less frequent episodes of apnea per hour (0.6 ± 0.7 vs 0.5 ± 0.7) and bradycardia per hour (1.2 ± 1.3 vs 0.9 ± 1.0) during nasal intermittent positive-pressure ventilation, these differences were not significant. There were no significant differences in the severity of these events as assessed by the duration and fall in transcutaneous oxygen pressure during apnea and heart rate during bradycardia. There were no significant changes in blood gases throughout the study. Nasal intermittent positive-pressure ventilation appears to have no advantages over nasal continuous positive airway pressure in preventing apnea and does not alter gas exchange in infants of less than 32 weeks of gestation.

(AJDC. 1989;143:1196-1198)

Continuous positive airway pressure (CPAP) by the nasal route is a useful adjunct to neonatal ventilatory management. It is widely used in the management of neonatal respiratory distress syndrome¹⁻³ and apnea of prematurity^{4,5}

as a method of weaning infants from ventilators.⁶

In addition to using CPAP by the nasal route, we have used intermittent positive-pressure ventilation (IPPV) by nasal prongs and nasopharyngeal tubes in infants of 32 weeks of gestation or less in an attempt to avoid intubation for apnea or respiratory failure. Despite scant evidence in the literature for this practice, a questionnaire sent to the directors of 19 tertiary care nurseries in Canada showed that 9 (53%) of 17 had also used nasal IPPV as a form of ventilatory support for these infants. While 3 of the latter respondents no longer used nasal IPPV, the remainder said they found it of benefit in clinical practice, particularly in managing infants with low birth weights (C.A.R., unpublished data, April 1986).

A prospective, randomized, crossover trial was therefore initiated to clarify the role of nasal IPPV by comparing its efficacy with that of nasal CPAP on gas exchange and apnea in infants of less than 32 weeks of gestation.

PATIENTS AND METHODS

Infants of 32 weeks of gestation or less by maternal dates or early obstetric ultrasound and who were treated by nasal CPAP for apnea of prematurity by the attending neonatologists were eligible for the study. Known causes of apnea were excluded. The infants were, without exception, receiving aminophylline and were in stable condition, except for their apneic episodes, at the time of study.

Both CPAP and nasal IPPV were delivered by a Baby Bird ventilator (Bird Corp, Palm Springs, Calif) at end-expiratory pressures of 4 cm H₂O during CPAP and peak pressures of 20 cm H₂O and end-expiratory pressures of 4 cm H₂O during nasal IPPV. These pressures were measured at the proximal end of the nasal prongs or nasopharyngeal tube by a pressure transducer (model MP45-4, Validyne Engineering Corp, Northridge, Calif) when the outlet was occluded. The ventilatory rate was set at 20 breaths per minute during nasal IPPV.

After obtaining informed parental consent, a baseline blood gas measurement while the infant was receiving CPAP was taken, and the infants were randomized to either CPAP or nasal IPPV according to a computer-generated randomization schedule. After receiving CPAP or nasal IPPV for 2 hours, a blood gas measurement was repeated. After receiving one mode for 6 hours (CPAP or nasal IPPV), a third blood gas measurement was taken and the infant was switched to the alternative mode. Two further blood gas determinations were taken after 2 and 6 hours on the alternative mode. In infants with indwelling arterial catheters, arterial blood gases were determined. "Arterialized" capillary gases were measured in the remaining infants, since, in well-perfused infants, arterialized capillary PCO₂ has an excellent correlation with arterial PCO₂.⁷ All infants were monitored with a transcutaneous PO₂ (tcPO₂) electrode (model 632, Roche Medical Electronics Inc, Everett, Mass) and the tcPO₂ at the time of the blood gas measurements, rather than the capillary PO₂ reading, was analyzed when a capillary gas measurement was taken.

The heart rate, respiratory impedance, tcPO₂, and proximal airway pressures were simultaneously recorded throughout the study on a four-channel recorder (model 7404A, Hewlett Packard Industrial Recorder, Medical Electronics Division, Waltham, Mass). At the end of the study period the tracings were analyzed, and the apnea attack rates with the infant receiving CPAP and nasal IPPV were documented. Significant apnea was defined as the cessation of spontaneous respirations for more than 15 seconds with an associated decrease in tcPO₂ of more than 5 mm Hg and/or a decrease in heart rate of more than 20% of the baseline heart rate. Significant bradycardia was defined as a decrease in heart rate of more than 20% of the baseline heart rate. Apnea and/or bradycardia that occurred during nursing interventions were not included in the study.

Based on previously published variability of apnea in infants of less than 32 weeks of gestation in this unit,⁸ 20 subjects were required, according to the tables of Machin and Campbell,⁹ to detect a 50% reduction in apnea with nasal IPPV compared with nasal CPAP at a power of 80% ($\alpha = .05$, one-tailed

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test). Statistical analysis of the means was performed with a paired Student *t* test (two-tailed test) and analysis of variance when more than 2 means were tested. $P < .05$ was considered significant and data are reported as mean \pm SD. The protocol was approved by the Clinical Investigation Committee of the Royal Alexandra Hospitals, Edmonton, Canada.

RESULTS

Demographic data on the 20 infants are presented in the following tabulation:

Value	Mean \pm SD (Range)
Birth Weight, g	923 \pm 292 (540-1600)
Gestation, wk	26 \pm 2 (22-32)
Weight at study, g	979 \pm 315 (530-1655)
Age at study, d	25.0 \pm 15.6 (3-56)

The mean fraction of inspired oxygen during the study was 0.29 ± 0.1 (range, 0.21 to 0.6). End-expiratory pressures measured at the proximal airway during nasal CPAP and IPPV varied from 2 to 4 cm H₂O, while the peak pressures during nasal IPPV varied from 8 to 21 cm H₂O, averaging approximately 10 cm H₂O.

The frequency and extent of apnea and bradycardia when comparing the 6-hour period that the infants were receiving nasal CPAP with a similar crossover period receiving nasal IPPV are presented in the Table. Although infants receiving nasal IPPV had slightly less frequent episodes of apnea and bradycardia per hour, these differences were not significant. In addition, there were no significant differences in the severity of these events as assessed by the duration and the fall in $tcPo_2$ during apnea and heart rate during bradycardia.

The $Paco_2$, Pao_2 , and alveolar-to-arterial oxygen gradient did not change significantly throughout the study. There were no significant differences in these values when comparing the period that the infants were receiving nasal CPAP with that when infants were receiving nasal IPPV (Table).

COMMENT

Our study was not designed to examine the efficacy of nasal CPAP in the management of apnea of prematurity,

Comparison Between Nasal CPAP and Nasal IPPV*		
	Nasal CPAP	Nasal IPPV
Apnea, No. of episodes per hour	0.6 \pm 0.7	0.5 \pm 0.7
Longest apnea episode, seconds	23 \pm 20	21 \pm 22
Greatest decrease in $tcPo_2$, mm Hg	17 \pm 15	14 \pm 11
Bradycardia, No. of episodes per hour	1.2 \pm 1.3	0.9 \pm 1.0
Greatest decrease in heart rate, beats per min	66 \pm 36	56 \pm 43
$Paco_2$ at 0 h, mm Hg	44 \pm 6	45 \pm 8
$Paco_2$ at 2 h, mm Hg	44 \pm 8	45 \pm 7
$Paco_2$ at 6 h, mm Hg	43 \pm 7	44 \pm 8
Pao_2 at 0 h, mm Hg	58 \pm 10	57 \pm 13
Pao_2 at 2 h, mm Hg	57 \pm 12	56 \pm 13
Pao_2 at 6 h, mm Hg	55 \pm 12	61 \pm 15

*Values are given as mean \pm SD. CPAP indicates continuous positive airway pressure; IPPV, intermittent positive-pressure ventilation. $tcPo_2$ indicates transcutaneous Po_2 .

because this form of therapy has already been shown to be advantageous.^{4,5} Rather, we were interested in seeing whether nasal IPPV was more effective than nasal CPAP in preventing apnea episodes in infants of less than 32 weeks of gestation. We have shown, in the present prospective randomized crossover trial, that nasal IPPV did not reduce the incidence of apnea, when compared with nasal CPAP, in this population. The choice of a 6-hour trial before and after crossover was arbitrary. This period needed to be long enough to document a minimum number of apnea episodes and yet not so prolonged as to introduce other variables, such as a natural improvement in the infants' condition over time.

Based on a sample size of 20 infants, we can be confident that a 50% or higher increase in the incidence of apnea during nasal IPPV was not missed by our study. Because infants ventilated with nasal prongs or face masks are 30 times more likely to suffer gastric perforations than infants ventilated with endotracheal tubes,¹⁰ we believed that such a reduction in the incidence of apnea would have been warranted to justify the continued use of nasal IPPV.

Although nasal CPAP has proved effective in the treatment of obstructive and mixed apnea,^{4,5} the mechanism of action has not been fully elucidated. It may involve improved oxygenation, altered respiratory reflexes, or both.¹¹⁻¹³ Hagan et al¹¹ have postulated that CPAP may stabilize the rib cage and so reduce inhibitory neural input to the respiratory control center. It may also act in reducing apnea incidence by improving oxygenation secondary to lung

inflation¹² or by eliminating the Hering-Breuer deflation reflex.¹³ It has also been suggested that its action is related to improved patency of the upper airway either by activation of dilator muscles or by passive splinting, thus reducing the incidence of obstructive apnea.^{5,14} We had postulated that nasal IPPV might enhance the latter effect by producing higher mean pharyngeal pressures and, in addition, might abort some apneic spells by the intermittent inflation of the hypopharynx, through a mechanism known as Head's paradoxical reflex.

It could be argued that nasal IPPV may have a more beneficial effect on obstructive apnea as opposed to centrally mediated apnea. Over 40% of apneic spells in premature infants are mixed or obstructive.⁸ Miller et al⁸ showed that CPAP reduces only obstructive and mixed apneic spells, with no effect on central apnea. We did not monitor nasal airflow in our study and thus were unable to differentiate between the various forms of apnea (central, obstructive, or mixed). It is impossible to distinguish between ventilator-generated air flow and spontaneous breaths with instruments used to determine the absence of airflow during obstructive apnea (eg, nasal thermistors or end-tidal carbon dioxide), especially during nasal IPPV.

Perhaps of less surprise in this study was the lack of support for nasal IPPV as a method of ventilation when compared with nasal CPAP in that no significant decrease in $Paco_2$ was observed during nasal IPPV. We found that peak airway pressure at the proximal airway during nasal IPPV was approximately

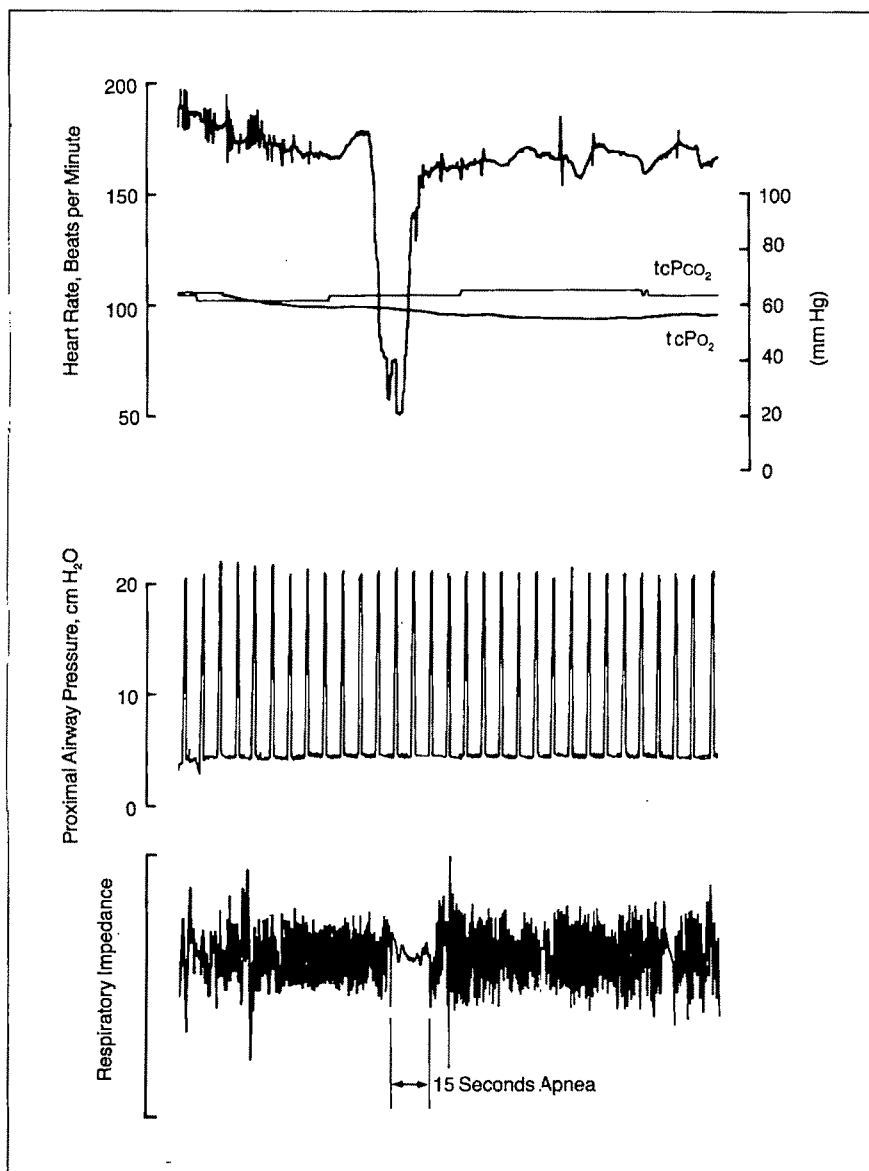


Illustration of bradycardia-associated apnea in an infant receiving nasal intermittent positive-pressure ventilation. Despite proximal airway pressures of 21 per 4 cm H₂O, no chest wall movement was detected on the respiratory impedance tracing, consistent with upper airway obstruction. tc indicates transcutaneous.

half the peak pressure when the outlet was occluded. Pharyngeal pressures during nasal CPAP are dependent on the presence of a seal between the tongue and soft palate.¹⁶ Nasal IPPV may thus have failed as a mode of ventilation in the current study, either because of poor transmission or attenuation of the applied pressure into the lungs. It may be possible to ventilate infants with pressures higher than those used in our study. However, we would not support this practice because the potential hazards of gastric distention and perforation far outweigh the risks of endotracheal intubation and ventilation.¹⁰

It is of interest to note that the peak pressures during IPPV were not transmitted to the chest wall during an apneic episode in one infant (Figure). No changes in respiratory impedance were observed in this tracing despite measured pressures of 21 per 4 cm H₂O at the proximal airway. This is consistent with the development of upper airway obstruction during an apneic episode. Gauda et al¹⁶ showed, by genioglossus electromyography, that premature infants with mixed and obstructive apnea are less apt to recruit their upper airway dilating muscles in response to spontaneous obstruction. We have observed that nasal IPPV, even at rela-

tively high pressures, did not relieve this obstruction.

We conclude that nasal IPPV at the rates and pressures employed in our study appears to have no advantages over nasal CPAP in preventing apnea of prematurity and does not reduce PaCO₂ in infants of less than 32 weeks of gestation. It may be associated with greater risks and is therefore not recommended as a mode of respiratory support in these infants.

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Pertussis in Neonates

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• Despite the increasing prevalence of pertussis in young adults and infants, reports of maternal-neonatal pertussis are rare. Our study involves three neonates who apparently acquired pertussis from their adolescent mothers. The diagnosis of pertussis was initially missed in all of the patients. The mothers had mild respiratory disease. All three newborns presented with life-threatening coughing and choking spells without a characteristic inspiratory whoop. Two neonates had apnea, bradycardia, cyanosis, and unresponsiveness, but were without the initial lymphocytosis that is distinctive of pertussis. These two neonates had a clinical course that was consistent with the historic "100-day-cough." They required prolonged ventilatory support and hospitalization at a high cost. The other neonate had a terminal pulmonary hemorrhage. Strategies for the early diagnosis, treatment, and prevention of this potentially lethal disease in neonates are discussed. (AJDC. 1989;143:1199-1202)

The prevalence of pertussis in infancy and early childhood has increased in recent years. Over 50% of all reported cases now occur in infants.^{1,2} Susceptible children have an attack rate of 81% from exposure to household contacts.³ Natural immunity to pertussis is lifelong, whereas 12 years after vaccination, 95% of the vaccinees are susceptible to pertussis.⁴ Adults and adolescents, especially females, with waning immunity and mild disease become the major reservoir for transmission of pertussis to unimmunized infants.² Seventy percent of the pertussis mortality occurs in infancy, with severe transient morbidity in many nonfatal cases.^{5,6} Although per-

tussis agglutinins are present in one third of maternal and neonatal serum samples, passive transplacental immunity does not reliably protect against neonatal infection.⁷

In this article, we describe three unusual maternal-neonatal patient-pairs with pertussis who presented to the Yale-New Haven (Conn) Hospital during a 1-year period. We also review the literature and highlight the strategies for the diagnosis, treatment, and prevention of this potentially lethal disease in neonates.

PATIENT REPORTS

PATIENT 1.— A full-term female infant was admitted to a community hospital in Connecticut at 26 days of age for increasing respiratory distress. The infant was examined four times at a local clinic for frequent coughing, choking, and poor feeding, which began at 20 days of life. Her 17-year-old mother was treated simultaneously with amoxicillin for a sore throat and a prolonged repetitive cough.

On hospital admission, the infant was afebrile, with a respiratory rate of 60 breaths per minute and a pulse rate of 200 beats per minute. There were moderate chest retractions and diffuse pulmonary crepitations. A chest roentgenogram revealed patchy peribronchial infiltrates radiating from the hila, with diffuse hyperinflation in both lung fields. The hemoglobin level was 111 g/L; hematocrit, 0.33; and white blood cell count, $63 \times 10^9/L$, with 0.26 segmented neutrophils, 0.26 band forms, 0.38 lymphocytes, 0.01 monocytes, 0.02 eosinophils, 0.03 myelocytes, and 0.04 metamyelocytes. Bacterial cultures of blood, cerebrospinal fluid, and urine were performed, and parenteral ampicillin sodium and gentamicin sulfate therapy commenced. Respiratory deterioration in the ensuing 24 hours led to admission to the Yale-New Haven Pediatric Intensive Care Unit.

On hospital arrival, the infant was intubated, afebrile, and in marked respiratory distress. Blood gases in 100% inspired oxygen showed a pH of 7.19, a PCO_2 of 67%, and a PO_2 of 98%. The white blood cell count was $92 \times 10^9/L$ (0.42 segmented forms, 0.22 band

forms, 0.10 lymphocytes, 0.06 atypical lymphocytes, 0.04 monocytes, 0.02 eosinophils, 0.05 myelocytes, 0.02 metamyelocytes, 0.02 promyelocytes, and 0.05 blasts). Platelet counts, partial thromboplastin time, and prothrombin time were elevated. Despite assisted ventilation, bradycardia, hypotension, and acidosis developed, and pulmonary compliance decreased. The hematocrit value fell from 0.30 to 0.16 within 4 hours. A chest roentgenogram showed increased bilateral consolidation and an enlarged cardiac silhouette. An electrocardiogram revealed the ST-wave changes of subendocardial ischemia. An echocardiogram showed an open foramen ovale, dilated right ventricle and right atrium, and poor contraction of the left ventricle. The infant died 12 hours after admission.

Postmortem examination revealed a fenestrated patent foramen ovale and an increased combined weight of both lungs (124 g). The cut surfaces showed atelectasis and extensive hemorrhage throughout the apex of the left lung. Histologic sections revealed bilateral pulmonary edema and focal hemorrhages, with diffuse infiltration by macrophages and moderate focal infiltration with inflammatory cells. The right lower lobe and entire left lung showed extensive necrotizing bronchopneumonia and thromboemboli.

Bordetella pertussis was isolated after 17 days from postmortem cultures of respiratory secretions and lung sections on Regan-Lowe medium and confirmed by fluorescent antibody staining. There were no other significant bacterial pathogens isolated.

PATIENT 2.— A male infant was one of dizygotic twins delivered at 36 weeks of gestation because of maternal preeclampsia. He was admitted to an outlying hospital at 21 days of age with a 1-day history of cough, coryza, vomiting, cyanosis, inactivity, and limpness followed by temporary cessation of respiratory efforts that responded to stimulation.

Examination revealed an afebrile infant with tachypnea and fine pulmonary rales. Occasional cough, cyanotic spells with apnea, and bradycardia were documented. Oxygen therapy as well as parenteral ampicillin and gentamicin therapy were commenced. Deterioration in respiratory status over 7 hours necessitated tracheal intubation and transfer to the Yale-New Haven Hospital Pediatric

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Intensive Care Unit. Blood gases in 100% inspired oxygen showed a pH of 7.25, a PO_2 of 73%, and a PCO_2 of 21.6%. The hemoglobin level was 148 g/L, the white blood cell count was $98 \times 10^9/L$ (0.41 segmented neutrophils, 0.09 band forms, 0.39 lymphocytes, 0.09 monocytes, and 0.03 atypical lymphocytes), and the platelet count was $513 \times 10^9/L$. He was hypoglycemic. Bacterial cultures of blood, cerebrospinal fluid, and urine were performed. Central apnea was diagnosed in view of the predominant findings of apnea and bradycardia, with a family history of sudden infant death syndrome in a 6-month old sibling.

The infant was intubated and underwent ventilation for 6 days. On extubation, apnea and bradycardia were again evident. Copious, thick nasopharyngeal secretions and collapse-consolidation in the right lung fields led to reintubation and ventilation 3 days later. The infant had a temperature of $39^\circ C$ on the 11th hospital day, with roentgenographic evidence of progressive right pulmonary consolidation and compensatory emphysema in the left lung. The white blood cell count was now $41 \times 10^9/L$ (0.27 segmented neutrophils, 0.32 band forms, 0.20 lymphocytes, 0.14 monocytes, 0.01 basophils, 0.04 atypical lymphocytes, and 0.02 metamyelocytes). The platelet count was $840 \times 10^9/L$.

The Pediatric Infectious Diseases Service of the Yale-New Haven (Conn) Hospital was consulted. The infant's 17-year-old mother had peripartum coryza-like symptoms, with severe repetitive protracted cough, which was suggestive of pertussis. *Bordetella pertussis* was later isolated from the infant's nasopharyngeal secretions and confirmed by a direct fluorescent antibody test. Erythromycin ethyl succinate was administered to the neonate and his close contacts. Oxacillin sodium and gentamicin were prescribed for the probability of secondary bacterial invaders. Respiratory isolation was begun. The infant was ventilator-dependent for 6 weeks. He received aerosolized ribavirin; his nasopharyngeal secretions were negative for respiratory syncytial virus by immunofluorescence, but he was treated because his twin sister (patient 3, discussed below) was infected with the virus. Chest roentgenograms after assisted ventilation revealed interstitial scarring. Apneic spells and cough resolved after 3 months. Weight gain continued below the fifth percentile for age because of vomiting and poor feeding. He had developmental delay. He was hospitalized for 4 months.

PATIENT 3.—The female sibling of patient 2 was admitted to the hospital 1 day after her twin brother. She was 22 days old, with a 1-day history of difficulty breathing, cyanosis, and one episode of respiratory cessation that responded to mouth-to-mouth resuscitation. On admission to the Yale-New Haven Pedi-

atric Intensive Care Unit, coughing spells, apnea, bradycardia, cyanosis, limpness, pallor, irregular and shallow respiratory efforts, and rales in the left lung were present. She required ventilatory support for 10 days. A chest roentgenogram revealed collapse-consolidation in the right upper lobe, with compensatory emphysema. The white blood cell counts on admission and on the eighth day, respectively, were 69 and $151 \times 10^9/L$ (0.48 segmented neutrophils, 0.03 band forms, 0.40 lymphocytes, 0.08 monocytes, and 0.01 eosinophils).

Evaluation by the Yale-New Haven Hospital Infectious Diseases Service on the 11th hospital day revealed a paroxysmal staccato cough characterized by 6 to 10 explosive bursts within one expiratory effort followed by apnea, bradycardia, and cyanosis. Coughing spells were initiated by any manipulation (eg, suctioning) and were followed by prostration, lethargy, and limpness. They were also associated with thick, tenacious respiratory secretions and were unaccompanied by an inspiratory whoop. Chest roentgenograms demonstrated progressive collapse-consolidation in the right lung fields with a corresponding mediastinal shift to the right and hyperaeration in the left lung fields. Nasopharyngeal secretions subsequently yielded *B pertussis*. Erythromycin therapy was discontinued because of gastrointestinal upset. Trimethoprim-sulfamethoxazole therapy was commenced instead. Mucus plug obstruction of a large airway led to a respiratory arrest. She was successfully resuscitated and required additional ventilatory support for 6 weeks. Respiratory syncytial virus was identified by immunofluorescent staining. Chest roentgenograms showed residual interstitial scarring. Apnea remitted at $2\frac{1}{2}$ months. She was discharged with persistent cough, developmental delay, and a weight below the fifth percentile after 3 months in the hospital.

COMMENT

These teenage mothers were the apparent point-source of pertussis in all 3 of the neonates described herein. Although the prevalence of pertussis in infancy has increased considerably in recent years, the scope of the problem of maternal-neonatal pertussis seems underestimated.

Neonatal pertussis was first reported in 1913 by Cockayne⁸ who described a 5-day-old neonate who contracted pertussis from family members; he also alluded in this article to Sir Thomas Watson, who reported that "the newcomer 'hooped on the first day he appeared in the world,'" and to Rilliet and Barthez,

who described another neonate who whooped on the first day of life. In 1921, Phillips⁹ described an obstetric nurse who infected 2 newborns under her care. Lapin,¹⁰ in 1943, described newborns with congenital pertussis in his book. Early reports of pertussis with onset at 4 to 7 days of life were also documented outside the English literature.¹¹⁻¹³ In none of these earlier neonates, however, was the diagnosis of pertussis proven. *Bordetella pertussis* was first isolated from a neonate in 1951.¹⁴ Linneman et al,¹⁵ in 1975, documented a hospital epidemic in which a 1-month-old infected a house officer, who subsequently passed on the disease to 6 newborns. Eleven of 400 patients with pertussis described by Nelson² in 1978 occurred in neonates; in 6 newborns, an adult was the source; in 2 newborns, the source was another child; and in 3 newborns, the source was unknown. McGregor and colleagues¹⁶ in 1984 described proven pertussis in three mother-infant pairs.

The pathophysiologic features of pertussis have been elucidated by the recognition of a protein exotoxin comprised of lymphocytosis-promoting factor, histamine-activating factor, and islet cell-activating factor.¹⁷ Some of the effects include entrapment of the lymphocytes within the vascular compartment, hypoglycemia, and abnormal function of the heart cells. The toxin also causes paralysis of the cilia of the respiratory epithelial cells, leading to increased mucus production and the characteristic cough. The fact that the disease continues unabated, despite antibiotic eradication of *B pertussis*, unless antibiotics are administered early in the catarrhal stage, strongly implicates the pertussis toxin in the pathogenesis of the disease.

After an incubation period of 5 to 14 days, the catarrhal phase of the illness begins. This is usually characterized by 1 to 2 weeks of upper respiratory tract symptoms and low-grade fever. This phase coincides with bacterial multiplication within the respiratory epithelium. This phase was characteristically contracted or absent in all three neonates discussed in the present article. The protein exotoxin, secreted by the bacteria, mediates the paroxysmal phase, which may last 6 to 14 weeks. This phase is usually characterized by

paroxysmal staccato coughing with an inspiratory whoop, which was absent in all three newborns. Instead, life-threatening coughing and choking spells followed by apnea, cyanosis, bradycardia, and unresponsiveness were the main symptoms. Increased mucus production that produced bronchial obstruction with alternating areas of pulmonary collapse-consolidation and emphysema as well as the roentgenographic features of perihilar shaggy infiltrates obscuring the heart border are also characteristic of this phase. A 2- to 3-week convalescent phase then follows.¹⁸ All three phases can be contracted in the neonate; although in the two neonates who survived, the course was consistent with the historic "100-day-cough."

The diagnosis of pertussis was significantly delayed in all three neonates, resulting in the late commencement of the specific control measures of respiratory isolation and erythromycin therapy for young adult pertussis-susceptible caretakers and to ill infants in the intensive care unit. First, the history and significance of maternal peripartum protracted cough was missed. Adults have waning vaccine-induced immunity and commonly present only with prolonged repetitive cough, instead of the full-blown pertussis syndrome with an inspiratory whoop and posttussive vomiting.^{19,20} At the time the infant presents with the illness, the adult's infection may have also progressed to the point where *B pertussis* can no longer be recovered by culture. Second, the absence of an inspiratory whoop was not recognized as a characteristic of neonatal pertussis. Third, although apnea, cyanosis, bradycardia, and unresponsiveness are typical of neonatal pertussis, the significance of paroxysmal cough and increased respiratory secretions were masked by ventilatory support and the presence of sudden infant death syndrome in a sibling. Fourth, the characteristic lymphocytosis that would have led to the suspicion of pertussis or would have supported the diagnosis of pertussis was absent in the early paroxysmal phase in the twins. This is a recognized feature of neonatal pertussis.^{21,22} Fifth, the laboratory diagnosis was further delayed in all of the infants by the presence of competing gram-negative flora that inhibited the growth of *B pertussis*. For

this reason, nasopharyngeal swabs or nasal washings are preferable to sputum or tracheal aspirates for the efficient isolation of this fastidious organism. Similar delays in the diagnosis of pertussis have led to nosocomial pertussis infection in two large hospital epidemics that involved medical personnel and other susceptible infants receiving intensive care.^{16,23}

Complications occur more frequently and with increased severity in the neonate. These include the interstitial bronchopneumonia of adenovirus, respiratory syncytial virus, or cytomegalovirus; any of these agents may coexist with *B pertussis*, as shown by the twins in our study, or may be the primary etiologic agent of the pertussis syndrome.^{16,24,25} Lobar pneumonia secondary to *Pneumococcus*, *Staphylococcus*, or hospital-acquired gram-negative organisms may be heralded by fever and leukemoid reaction with blasts in the peripheral blood, as well as by the clinical and roentgenographic evidence of progressive pneumonic consolidation; lobar pneumonia is the usual cause of death.²¹ Bronchiectasis, pneumothorax, and pneumomediastinum also occur. Respiratory arrest from airway obstruction by a mucus plug was evident in the second newborn. This complication is another cause of sudden death. Other complications include convulsions from asphyxia, subarachnoid hemorrhage, encephalopathy, cortical atrophy, and hypoglycemia. Severe and prolonged hypoglycemia was present initially in the second newborn and might have been the direct effect of the pertussis toxin. Developmental delay was present in the twins in our study. This may result from the multiple central nervous system complications or from prolonged hospitalization and ventilatory support without adequate stimulation. Repeated vomiting leads to hypocalcemic tetany, metabolic acidosis, dehydration, and malnutrition, as was present in the twins; hernias and prolapse of the rectum may also occur. Increased venous pressure from the vomiting and coughing results in petechiae and subconjunctival and intracranial hemorrhages.⁸ To our knowledge, a bleeding diathesis with terminal pulmonary hemorrhage in a neonate with pertussis (patient 1) has not been previous-

ly reported.

Prevention of perinatal pertussis is aided by efficient patient diagnosis and infant immunization. A 14-day course of erythromycin administered early in the catarrhal phase shortens the period of communicability^{26,27} and may modify the course of the illness. Close contacts may be protected by erythromycin therapy and active immunization—especially for those with chronic lung disease. Trimethoprim-sulfamethoxazole is the substitute therapy for patients with erythromycin intolerance.²⁷ Close contacts who have not completed the primary diphtheria and tetanus toxoids and pertussis vaccine series plus a booster appropriate for age and those who have not received this vaccine within 3 years of exposure should be given a dose of the vaccine.²⁷ During a pertussis epidemic, the vaccine may be given to infants at 1 month of age.⁷ The pertussis vaccine is not recommended for routine adult immunization. Respiratory isolation should be instituted for 5 days during antibiotic therapy. Treatment or prophylaxis with pertussis immunoglobulin was abandoned when controlled trials showed no benefit.²⁸

Three newborns who apparently acquired pertussis from their teenage mothers are described. Young adults with waning immunity and mild atypical disease are the source of infection to susceptible infants. Neonatal pertussis is rarely associated with the characteristic whoop or lymphocytosis. Instead, newborns present with life-threatening coughing spells associated with apnea, bradycardia, cyanosis, and unresponsiveness. Complications require prolonged, costly hospitalization and ventilatory support. Early patient identification, antimicrobial chemotherapy to the index patient and to exposed medical and household contacts, as well as immunization for susceptible infants during epidemics are necessary to prevent this potentially lethal disease.

Since the initial submission of this report in February 1989, we have treated a 5-month-old unimmunized infant whose parents had a 1-month history of "bronchitis" that was unresponsive to antibiotic therapy. This infant presented with apneic spells, fever, and cough without paroxysms or whoop. She de-

veloped a leukemoid reaction of $85 \times 10^9/L$ white blood cells, with blasts in the peripheral blood and died of an overwhelming pneumonia. *Bordetella pertussis* was isolated from the respiratory secretions before death and from a specimen of hemorrhagic lung at autopsy.

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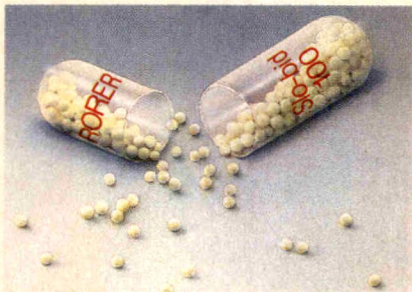
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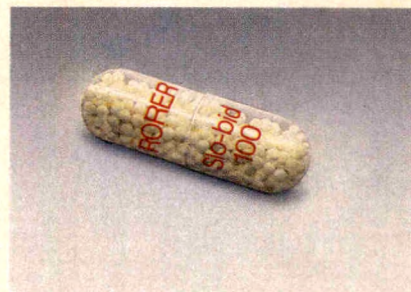
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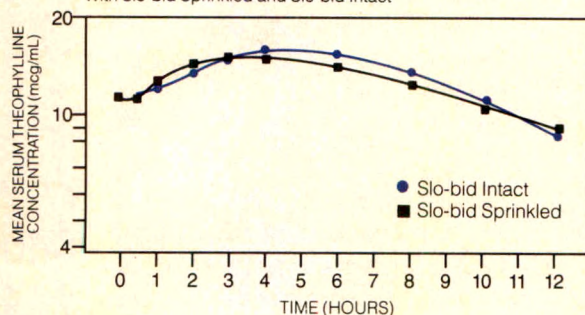
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References: 1. Saccar CL, Gawchik S, Spitzer I, et al: Steady-state evaluation of sustained-release theophylline administered in apple-sauce in asthmatic children. *Immunol Allergy Pract* 1987;9:462-466. 2. Consumer attitudes toward solid forms of medication. Capsugel, Division of Warner-Lambert Company, March 1983.

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BRIEF SUMMARY

DESCRIPTION: Slo-bid™ Gyrocaps® contain 50 mg, 75 mg, 100 mg, 125 mg, 200 mg, or 300 mg theophylline anhydrous in the form of long-acting beads within a dye-free hard gelatin capsule and are intended for oral administration. Slo-bid Gyrocaps can be administered with a 12-hour dosing interval for a majority of patients and a 24-hour dosing interval for selected patients (see DOSAGE AND ADMINISTRATION section in full prescribing information for description of appropriate patient population).

INDICATIONS AND USAGE: For relief and/or prevention of symptoms from asthma and reversible bronchospasm associated with chronic bronchitis and emphysema.

CONTRAINDICATIONS: Slo-bid is contraindicated in individuals who have shown hypersensitivity to any of the components of this product. It is also contraindicated in patients with active peptic ulcer disease and in individuals with underlying seizure disorders (unless receiving appropriate anticonvulsant medication).

WARNINGS: Serum levels above 20 µg/mL are rarely found after appropriate administration of the recommended doses. However, in individuals in whom theophylline plasma clearance is reduced for any reason, even conventional doses may result in increased serum levels and potential toxicity. Reduced theophylline clearance has been documented in the following readily identifiable groups: 1) patients with impaired renal or liver function; 2) patients over 65 years of age, particularly males and those with chronic lung disease; 3) those with cardiac failure from any cause; 4) patients with sustained high fever; 5) neonates and infants under 1 year of age; and 6) those patients taking certain drugs (see PRECAUTIONS, Drug Interactions). Frequently, such patients have markedly prolonged theophylline serum levels following discontinuation of the drug.

Reduction of dosage and laboratory monitoring is especially appropriate in the above individuals.

Serious side effects such as ventricular arrhythmias, convulsions, or even death may appear as the first sign of toxicity without any previous warning. Less serious signs of theophylline toxicity (i.e., nausea and restlessness) may occur frequently when initiating therapy but are usually transient, when such signs are persistent during maintenance therapy they are often associated with serum concentrations above 20 µg/mL. Stated differently, *serious toxicity is not reliably preceded by less severe side effects*. A serum concentration measurement is the only reliable method of identifying a potential for life-threatening toxicity.

Many patients who require theophylline exhibit tachycardia due to their underlying disease process, so the cause/effect relationship to elevated serum theophylline concentrations may not be appreciated.

Theophylline products may cause dysrhythmia and/or worsen preexisting arrhythmias and any significant change in rate and/or rhythm warrants monitoring and further investigation.

Studies in laboratory animals (minipigs, rodents, and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

PRECAUTIONS: General: On the average, theophylline half-life is shorter in cigarette and marijuana smokers than in nonsmokers, but smokers can have half-lives as long as nonsmokers. Theophylline should not be administered concurrently with other xanthine preparations. Use with caution in patients with hypoxemia, hypertension or with a history of peptic ulcer. Theophylline may occasionally act as a local irritant to the GI tract, although GI symptoms are more commonly centrally mediated and associated with serum drug concentrations over 20 µg/mL.

Information for Patients:

The physician should reinforce the importance of taking only the prescribed dose at the prescribed time intervals. The patient should alert the physician if symptoms occur repeatedly, especially near the end of a dosing interval. When prescribing administration by the sprinkle method, details of the proper technique should be explained to the patient.

Laboratory Test: Serum levels should be monitored periodically to determine the theophylline levels associated with observed clinical response and to identify the potential for toxicity. For such measurements, the serum sample should be obtained at the time of peak concentration, approximately 5-9 hours after the morning dose. It is important that the patient has not missed or taken additional doses during the previous 48 hours and that dosing intervals have been reasonably equally spaced.

DOSE ADJUSTMENT BASED ON SERUM THEOPHYLLINE MEASUREMENTS WHEN THESE INSTRUCTIONS HAVE NOT BEEN FOLLOWED MAY RESULT IN RECOMMENDATIONS THAT PRESENT RISK OF TOXICITY TO THE PATIENT.

Drug Interactions:

Drug-Drug: Toxic synergism with ephedrine has been documented and may occur with some other sympathomimetic bronchodilators. In addition, the following drug interactions have been demonstrated:

Theophylline with:	Increased serum theophylline levels
Allopurinol (high dose)	Increased serum theophylline levels
Cimetidine	Increased serum theophylline levels
Erythromycin, Troleandomycin	Increased renal excretion of lithium
Lithium carbonate	Increased serum theophylline levels
Oral contraceptives	Decreased theophylline and phenytoin serum levels
Phenytoin	Decreased serum theophylline levels
Rifampin	

Drug-Food: Taking Slo-bid immediately after a high-fat content meal such as 8 ounces whole milk, 2 fried eggs, 2 strips bacon, one bran muffin with butter, 2 ounces hash brown potatoes (about 750 calories, including approximately 49 gm of fat) may result in a decrease in the rate of absorption, but with no significant difference in the extent of absorption (see CLINICAL PHARMACOLOGY, Pharmacokinetics). The influence of the type and amount of other foods, as well as the time interval between drug and food, has not been studied.

Drug/Laboratory Test Interactions: Currently available analytic methods, including high-pressure liquid chromatography and immunoassay techniques, for measuring serum theophylline levels are specific. Metabolites and other drugs generally do not affect the results. Other new analytic methods are also now in use. The physician should be aware of the laboratory method used and whether other drugs will interfere with the assay for theophylline.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies have not been performed with theophylline.

Chromosome-breaking activity was detected in human cell cultures at concentrations of theophylline up to 50 times the therapeutic serum concentrations in humans. Theophylline was not mutagenic in the dominant lethal assay in male mice given theophylline intraperitoneally in doses up to 30 times the maximum daily human oral dose.

Studies to determine the effect on fertility have not been performed with theophylline.

Pregnancy: Pregnancy Category C.—Animal reproduction studies have not been conducted with theophylline. It is also not known whether theophylline can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Theophylline should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Theophylline is distributed into breast milk and may cause irritability or other signs of toxicity in nursing infants. Because of the potential for serious adverse reactions in nursing infants from theophylline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:

Safety and effectiveness of Slo-bid Gyrocaps administered:

1. Every 24 hours in children under 12 years of age, have not been established.
2. Every 12 hours in children under 6 years of age, have not been established.

ADVERSE REACTIONS: The following adverse reactions have been observed, but there has not been enough systematic collection of data to support an estimate of their frequency. The most consistent adverse reactions are usually due to overdose.

Gastrointestinal: nausea, vomiting, epigastric pain, hematemesis, diarrhea.

Central Nervous System: headaches, irritability, restlessness, insomnia, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions.

Cardiovascular: palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, ventricular arrhythmias.

Respiratory: tachypnea.

Renal: potentiation of diuresis.

Other: alopecia, hyperglycemia, inappropriate ADH syndrome, rash.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription. Keep this and all medications out of the reach of children.

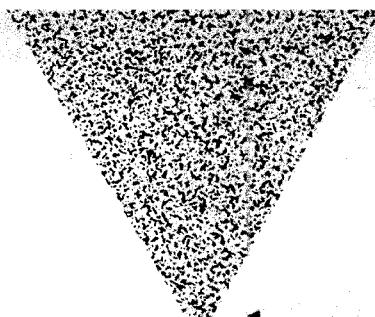
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- 125 mg—Opaque white (cap) and opaque white (body) capsule with 125 printed in red
- 200 mg—Opaque white (cap) and clear (body) capsule with 200 printed in red
- 300 mg—Opaque white capsule with 300 printed in red

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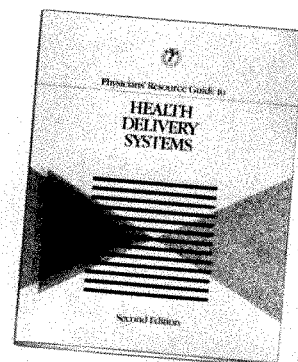
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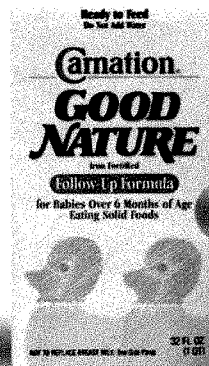
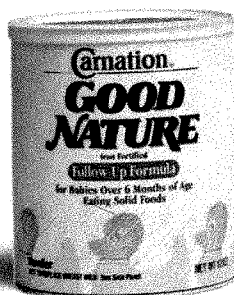
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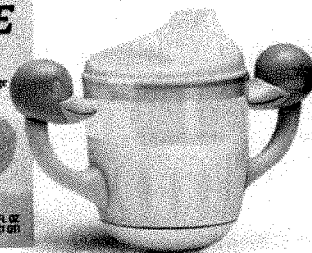
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Radiological Cases of the Month

Alain Martinot, MD; Francis Leclerc, MD; Martine Remy-Jardin, MD; Jean Darras, MD;
Michel Chenaud, MD; Lionel Wattinne, MD (*Contributors*); Beverly P. Wood, MD (*Section Editor*)

Figure 1.

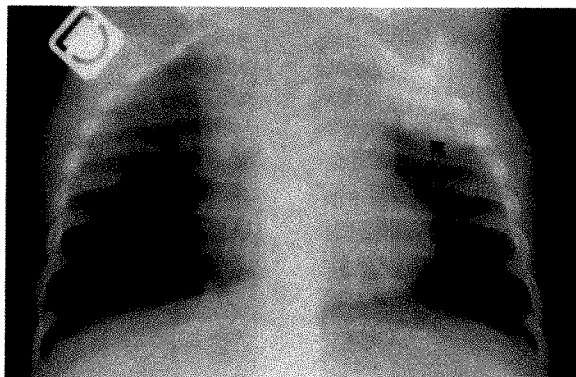


Figure 2.

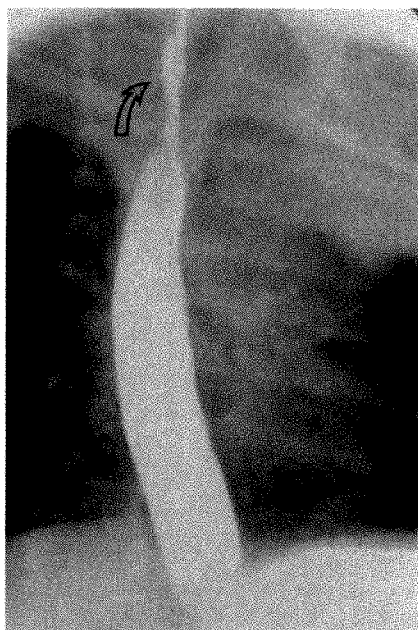


Figure 3.



A previously healthy 12-month-old girl had a 3-day history of fever (temperature, 40°C), sore throat, dysphagia, and vomiting. Physical examination revealed 2 × 3-cm left cervical adenopathy and hepatosplenomegaly. No focal infection was identified.

Admission chest roentgenogram was normal. White blood cell count was $12.5 \times 10^9/L$ (0.52 neutrophils); C-reactive protein level was elevated (294 mg/L). Cerebrospinal fluid and

urinalysis findings were normal. Three blood cultures yielded *Staphylococcus aureus*, methicillin sodium-susceptible.

Despite antibiotic treatment with vancomycin hydrochloride, rifampin, and amikacin sulfate, she remained febrile with positive blood cultures for 3 days. There was no dyspnea or dysphagia. On the third day after admission, a chest roentgenogram was abnormal (Fig 1). A left posterior oblique

chest roentgenogram (Fig 2) and lateral neck roentgenogram (Fig 3) with barium swallow were obtained.

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Contributed from the Departments of Pediatrics (Drs Martinot, Leclerc, and Chenaud), Otorhinolaryngology (Dr Darras), and Radiology (Drs Remy-Jardin and Wattinne), Centre Hospitalier Universitaire de Lille (France), Hôpital Calmette.

Reprint requests to Department of Radiology, PO Box 648, University of Rochester Medical Center, 601 Elmwood Ave, Rochester, NY 14642 (Dr Wood).

Denouement and Discussion

Extrapleural Effusion of Retropharyngeal Origin

Fig 1.—Posteroanterior chest roentgenogram showing a left extrapleural opacity (arrow) widening the upper mediastinum.

Fig 2.—Left posterior oblique chest roentgenogram with barium in the esophagus showing a left mediastinal/extrapleural opacity and narrowing of the esophagus in the upper thorax (arrow).

Fig 3.—Lateral neck roentgenogram showing increased width of the retropharyngeal soft tissues (R), reversal of the cervical spine lordosis, and anterior displacement of the upper esophagus.

The diagnosis of cervicoextrapleural and cervicomediastinal extension of a retropharyngeal abscess was suspected. With the patient under general anesthesia, the posterior pharyngeal wall appeared normal, but digital palpation revealed a fluctuant mass. A large amount of purulent material was drained by incision of the posterior pharyngeal wall, and the next day chest and lateral neck roentgenograms showed resolution of both the extrapleural and mediastinal effusions and disappearance of the retropharyngeal thickening. Antibiotic treatment was discontinued after 21 days, and the patient was discharged in good health.

Downward propagation via the retrovisceral space of a retropharyngeal abscess is extremely rare since the advent of antibiotics.¹⁻³ This retrovisceral space is the major pathway of oropharyngeal infection spread to the neck and mediastinum.¹ Behind the esophagus and anterior to the prevertebral fascia, the retrovisceral space

extends upward to the base of the skull and inferiorly into the posterior mediastinum. The cervical space is in continuity with the retropharyngeal space through the thin alar fascia. At the thoracic inlet there is anatomic correspondence with Sibson's fascia, a tent-shaped layer attached to the lower cervical spine and upper ribs, which allows extrapleural spread of an abscess.

The diagnosis of retropharyngeal abscess may be difficult in very young children.⁴ In this patient, dysphagia disappeared rapidly after admission and there was no respiratory difficulty, noisy breathing, or visible swelling of the posterior pharyngeal wall. Cervical lymphadenopathy suggested the diagnosis. Lateral neck views were obtained and barium swallow was performed because of the noted widening of the upper mediastinum.

Recommendations follow:

1. In cases of retropharyngeal abscess, a search for cervicoextrapleural and cervicomediastinal extension by

repeated chest roentgenograms should be performed. Computed tomographic scan with contrast will differentiate between cellulitis and abscess and identify the site and extent of abscess formation.

2. In cases of unexplained upper thoracic extrapleural effusion or widened mediastinum, one must search for a retropharyngeal abscess even in the absence of dysphagia, dyspnea, or swelling of the posterior pharyngeal wall. Lateral neck roentgenography, computed tomography, barium swallow, and ultrasound are the best procedures to detect a retropharyngeal abscess.⁴

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The Editors welcome contributions to PICTURE OF THE MONTH and RADIOLOGICAL CASE OF THE MONTH. Those who wish to contribute should send their manuscripts to Dr Feingold (Picture of the Month), National Birth Defects Center, Franciscan Children's Hospital, 30 Warren St, Brighton, MA 02135, or Dr Wood (Radiological Case of the Month), University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.

Carl H. Gumbiner, MD; John P. Cheatham, MD; Larry A. Latson, MD; David A. Danford, MD;
John D. Kugler, MD; Philip J. Hofschire, MD (*Contributors*); Beverly P. Wood, MD (*Section Editor*)

A 3-week-old male infant was seen for routine evaluation. His parents reported no problems other than decreased

feeding for 4 to 5 days. The infant was mildly pale and tachypneic. His weight was 3700 g (60 g above birth weight). Respirations were 70/min. There was a grade 2/4 systolic ejection murmur at the upper left sternal border. Pulses were normal. He was referred for further diagnostic studies, including a chest roentgenogram (Fig 1), an echocardiogram (Fig 2), magnetic resonance imaging (Fig 3), and angiography (Fig 4).

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Contributed from the Department of Pediatric Cardiology, University of Nebraska Medical Center, Omaha.
Reprint requests to Department of Radiology, PO Box 648, University of Rochester Medical Center, 601 Elmwood Ave, Rochester, NY 14642 (Dr Wood).

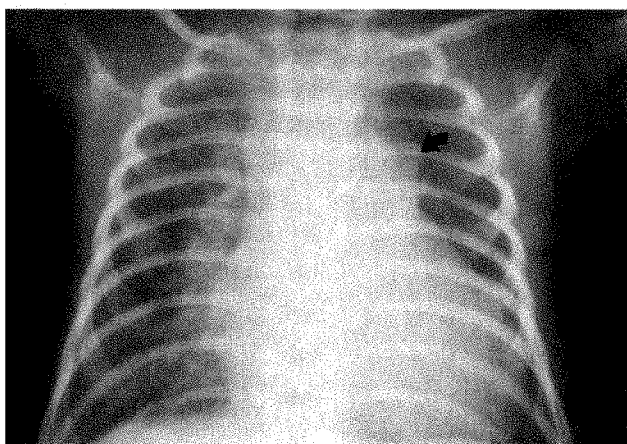


Figure 1.

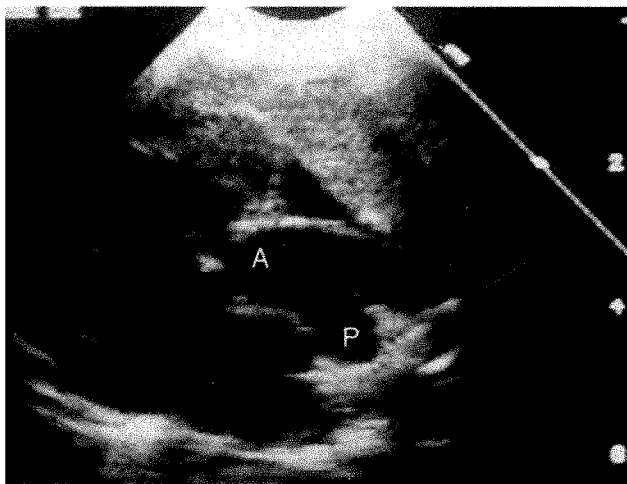


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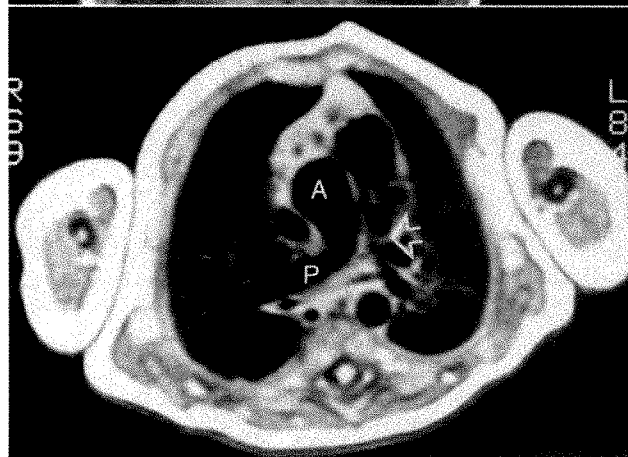
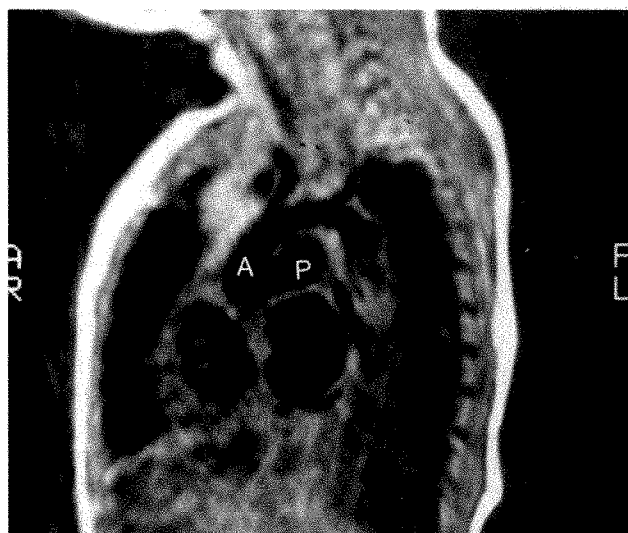


Figure 3.

Anomalous Origin of the Right Pulmonary Artery From the Aorta: 'Hemitruncus'

Fig 1.—Chest roentgenogram showing cardiomegaly with prominent main pulmonary artery segment (arrow) and increased pulmonary vascular markings, more prominent on the right side than on the left side.

Fig 2.—Two-dimensional echocardiogram. Suprasternal notch view shows the right pulmonary artery (P) arising posteriorly from the ascending aorta (A).

Fig 3.—Magnetic resonance image in sagittal plane (top) and axial plane (bottom) demonstrating the origin of the right pulmonary artery (P) from the aorta (A). The axial plane image also demonstrates the left pulmonary artery (arrow) and its attachment to the main pulmonary trunk.

Fig 4.—Main pulmonary arteriogram demonstrates the continuity of the main pulmonary trunk (P) with the left pulmonary artery (L). The catheter balloon tip is inflated in the patent ductus arteriosus, obstructing the flow of contrast into the aorta.

Hemitruncus is an unusual cardiovascular malformation in which one pulmonary artery, usually the right,¹ arises from the ascending aorta, while the opposite pulmonary artery connects normally to the main pulmonary trunk. An associated patent ductus arteriosus is common,² and intracardiac defects are occasionally present.^{1,2} The diagnosis must be applied cautiously to avoid confusion with conditions in which one pulmonary artery is absent and circulation to that lung is supplied via a systemic collateral vessel.¹

As a result of this anatomic malformation, systemic venous return in its entirety is directly through a single pulmonary artery, usually the left, while the contralateral lung is perfused with systemic arterial blood (a left-to-right shunt).¹⁻⁵ Pulmonary hypertension is present in both lungs, but the pathologic abnormality of the small pulmonary arteries may differ on the two sides.⁶ Embryologically, the defect is felt to result from defective development of the conotruncal ridges.^{1,3}

The condition manifests in infancy with signs and symptoms of congestive heart failure. The plain chest roentgenogram may not suggest the diagnosis. Radionuclide angiography

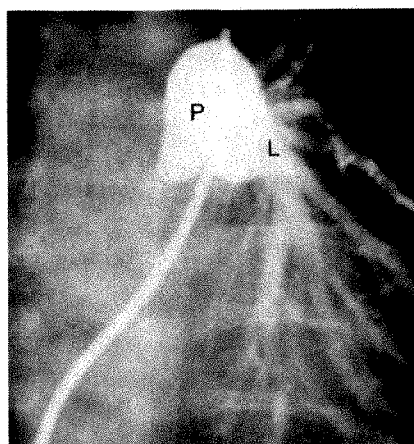


Figure 4.

is helpful.⁷ Computed tomography,⁸ echocardiography,^{9,10} and magnetic resonance imaging may all be diagnostic. Cardiac catheterization and angiography are performed for the assessment of hemodynamics and the exclusion of associated defects.

Treatment consists of relocation of the anomalous pulmonary artery from the aorta to the pulmonary trunk, either directly or with the use of a graft.¹⁻³ Surgery should be performed promptly in infancy for the alleviation of symptoms and the prevention of

progressive pulmonary vascular disease.

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Antihistamines are contraindicated in patients hypersensitive to the drug or to other antihistamines of similar chemical structure (see **PRECAUTIONS — Drug Interactions** in a complete package insert).

Antihistamines should not be used in newborn or premature infants. Because of the higher risk of antihistamines for infants generally and for newborns and premature infants in particular, antihistamine therapy is contraindicated in nursing mothers (see **PRECAUTIONS — Nursing Mothers** in a complete package insert).

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Antihistamines should be used with considerable caution in patients with: narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, and bladder neck obstruction.

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The most frequent adverse reactions are underlined:

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Gastrointestinal System: Epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.

Respiratory System: Thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness.

Cardiovascular System: Hypotension, headache, palpitations, tachycardia, extrasystoles.

Hematologic System: Hemolytic anemia, thrombocytopenia, granulocytosis.

Genitourinary System: Urinary frequency, difficult urination, urinary retention, early menses.

General: Urticaria, drug rash, anaphylactic shock, photosensitivity, excessive perspiration, chills, dryness of mouth, nose and throat.

DOSAGE AND ADMINISTRATION

DOSAGE SHOULD BE INDIVIDUALIZED ACCORDING TO THE NEEDS AND RESPONSE OF THE PATIENT.

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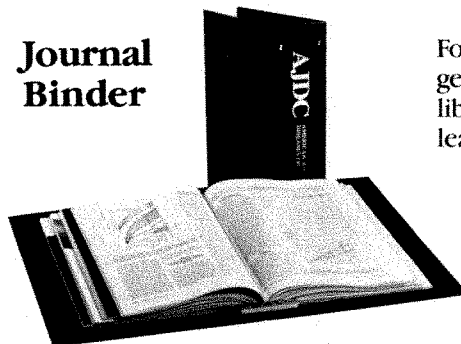
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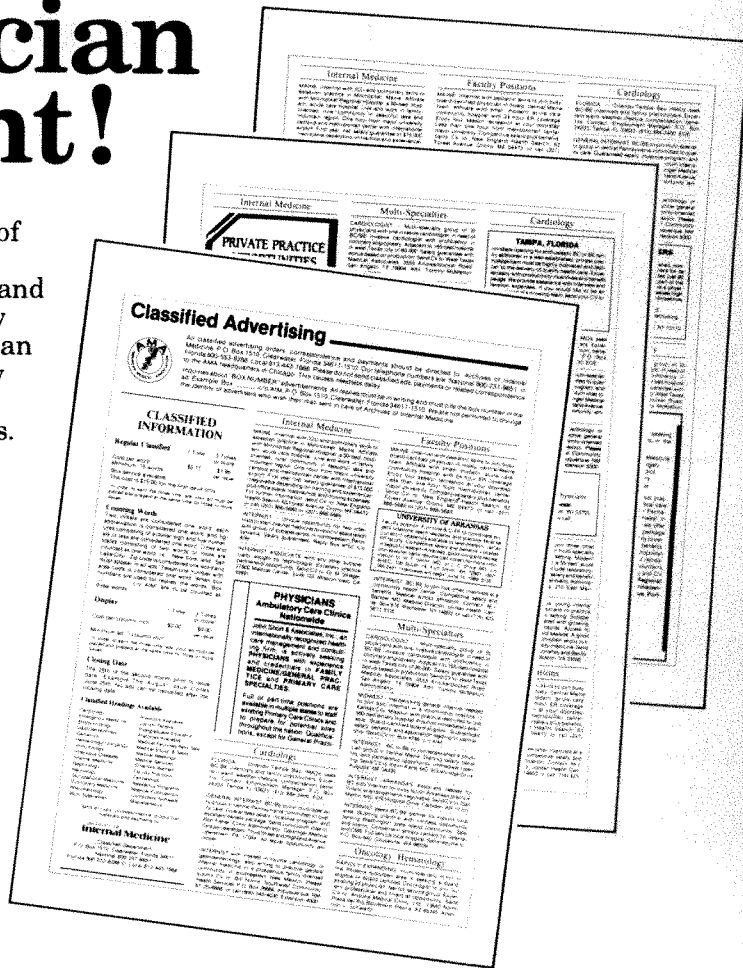
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Short-term Memory Impairment in Cannabis-Dependent Adolescents

Richard H. Schwartz, MD; Paul J. Gruenewald, PhD; Michael Klitzner, PhD; Paul Fedio, PhD

• The concentration of Δ -9-tetrahydrocannabinol in marijuana available in the United States has increased by 250% since investigations of the effects of marijuana on short-term memory first appeared in scientific journals. Moreover, previous investigations of short-term memory in long-term marijuana smokers involved adults only. We evaluated the auditory/verbal and visual/spatial memory of 10 cannabis-dependent adolescents and compared the results with performance of 17 subjects in two control groups. The control groups included 8 adolescent drug abusers who had not been long-term users of cannabis and another 9 adolescents who had never abused any drug. All three groups were matched on age, IQ, and absence of previous learning disabilities. Adolescents with a history of frequent alcohol or phencyclidine abuse were excluded from entering the study. A

battery of seven neuropsychological tests was administered initially to all subjects and a parallel test battery was administered 6 weeks thereafter. Significant differences between the cannabis-dependent group and the two control groups were obtained initially on the Benton Visual Retention Test ($F[2,24] = 6.07$) and the Wechsler Memory Scale Prose Passages ($F[2,23] = 7.04$). After 6 weeks of supervised abstinence from intoxicants, subjects in the cannabis-dependent group showed some significant improvement on the Wechsler Memory Prose Passages score and on the Benton Visual Retention Test; however, the improvement failed to achieve statistical significance. We concluded that cannabis-dependent adolescents have selective short-term memory deficits that continue for at least 6 weeks after the last use of marijuana.

(AJDC. 1989;143:1214-1219)

ers were found to react more slowly on perceptuomotor tasks, such as the Pencil Tapping Test. When the scores of all the memory tests were combined, there was no difference between the score of the cannabis-dependent group and that of the control group. However, statistically significant differences were noted for the individual tests of short-term (recent) memory, with the cannabis-dependent individuals scoring much lower.

The potency of drug-quality cannabis has been steadily increasing, averaging 3.65% Δ -9-tetrahydrocannabinol (Δ -9-THC) in 1987 vs 1.5% Δ -9-THC a decade ago.¹⁵ Sinsemilla, the highly potent seedless variety of marijuana preferred by many users (including the cannabis-dependent teenagers in the present study), averages 7% Δ -9-THC; as such, it is approximately twice as potent as the hashish available in the United States.¹⁶ Given these trends alone, a reevaluation of the effects of long-term cannabis use on short-term memory seemed to us justified and long overdue. The need for such a study was, moreover, confirmed by personal observation.

The pilot study reported here differs in several important ways from past research efforts.^{16,17} Unlike most past studies, the current study focuses on an American middle-class adolescent population with at least 8 years of education. We had observed that cannabis-dependent adolescents who have just entered a drug-abuse treatment program experience difficulties in recalling newly learned program rules and traditions as well as remembering who said what in a large group therapy setting. These adolescents report that such deficiencies persist for at least 3 or 4 weeks after their last use of cannabis. Their observations were the immediate impetus for this study.

Studies of the effects of long-term cannabis use conducted during the late 1960s, 1970s, and early 1980s inconsistently demonstrated memory impairment.¹⁻¹² Efforts to evaluate possible short-term memory impairment in cannabis-dependent individuals always involved adult subjects, and were usually conducted in North African, Asian, Caribbean, or Central American countries. Investigations conducted in Egypt⁴⁻⁸ and India,⁹⁻¹² for example, found that cannabis dependence was associated with abnormal Bender Gestalt Test and/or Wechsler Memory Scale scores. Satz and colleagues,³ who studied 41 cannabis-dependent Costa Rican

adults and 41 matched controls, initially found no significant differences on seven tests of neuropsychological functioning, including the Wechsler Adult Intelligence Scale and the Benton Visual Retention Test. However, Page and coauthors,¹³ in conducting a follow-up study, retested 27 of the 41 original cannabis-dependent subjects and 30 of the 41 matched original controls and found that the majority of the former group demonstrated reduced capacity for sustained attention and significant impairment of short-term memory on three of the seven neuropsychological tests. The cannabis-dependent subjects also had slower rates of processing and performance on self-paced measures that required sustained attention.

Clinical reports of the negative effects of long-term marijuana use on performance of skilled tasks and on motivation continue to appear in the literature. Varma and coworkers¹⁴ administered a battery of 13 psychological tests to 26 cannabis-dependent Indian adults and 26 matched controls. The cannabis use-

Accepted for publication April 20, 1989.

From the Department of Pediatrics, Georgetown University School of Medicine, Washington, DC (Dr Schwartz); Prevention Research Center, Berkeley, Calif (Dr Gruenewald); Pacific Institute for Research and Evaluation, Vienna, Va (Dr Klitzner); and Neuropsychology Section, National Institutes of Health, Bethesda, Md (Dr Fedio).

Presented at the 28th Annual Meeting of the Ambulatory Pediatric Association, Washington, DC, May 1988.

Reprints not available.

STUDY DESIGN AND PATIENT POPULATION

Patient Population

The 10 study subjects and 8 of the 17 controls were drawn from patients enrolled in a modified outpatient therapeutic community drug-abuse treatment program for adolescents in suburban Washington, DC. Participants were primarily white, middle-class adolescents whose median age was 16 years. A large majority were residing with their parents before entering the treatment facility and were convinced by parental pressure to enter treatment for chemical dependency. During the first 90 days after entering treatment, the patients remained in the facility during the day and early evening. They ate dinner and slept at the home of another adolescent in treatment who, because of his or her progress in the program, has earned trusted status. The average duration of stay in the treatment facility is 14 to 15 months. The parents of the subjects and those of the adolescents in the two control groups in our study were representative of those of other program participants. They are typically well educated (approximately 50% of the fathers hold college degrees), and many have professional or administrative jobs.

Inclusion Criteria

Criteria for inclusion in the study were (1) age 14 through 16 years; (2) an IQ between 90 and 125; (3) absence of childhood learning disabilities or hyperactivity, as determined by queries to participants, their parents, and a review of a photocopy of the sixth-grade report card; (4) alcohol intoxication less than weekly before entering the treatment facility and no record of chronic alcohol intoxication; (5) infrequent use (no more than 15 times) of phencyclidine, which is believed to impair short-term memory in persons who smoke it frequently¹⁸; and (6) no history of a prior seizure disorder, concussion, or psychosis.

No subject was taking any prescribed or illicit psychoactive medication during the study. Inclusion and exclusion criteria were verified by one of us (R.H.S.) after interviews with parents and receipt of photocopies of an upper elementary school report card.

Institutional Review Board Approval

Approval for this voluntary study was obtained from the Institutional Review Board of Georgetown University School of Medicine, Washington, DC. Oral and written consent was obtained from 27 participants and their parents. Withdrawal from the study was permitted at any time. Four cannabis-dependent subjects or their parents refused

to participate in the study, and 4 others who began the study were later excluded because their IQ scores fell outside study criteria.

Study Groups

A total of 27 participants met all study criteria. These 27 individuals represented three types of adolescents—cannabis-dependent adolescents (group A), drug-free adolescents (group B), and adolescent patients at the Straight Incorporated treatment facility, Springfield, Va, who had abused drugs but who had not been cannabis dependent (group C).

Group A.— Group A consisted of 10 adolescents (9 male, 1 female) admitted to the treatment facility between October 1985 and August 1986. Each of these individuals was interviewed by one of us (R.H.S.), and was found to fulfill *Diagnostic and Statistical Manual of Mental Disorders, Third ed*, criteria for cannabis dependence. All had smoked marijuana that they believed to be of high potency (mean, 18 g/wk) at least 4 days per week (mean, 5.9 d/wk) for at least 4 consecutive months—to within a few days of their admission to treatment (mean, 7.6 months). The 12-month prevalence of drinking alcoholic beverages to intoxication ranged from 0 to 35 times (mean, 19 episodes per year). Lifetime use of phencyclidine ranged from 0 to 15 times, with a mean use of 3.6 times.

Group B.— Group B consisted of nine adolescent volunteers (six males, three females), who were drug free. Adolescents in group B were individually interviewed in depth by a program staff member, and none had taken any drugs at any time with the possible exception of infrequent experimentation with alcohol, but not to drunkenness. They were matched to program participants in terms of socioeconomic status, home environment, parents' education, and IQ.

Group C.— Group C consisted of eight adolescents (three males, five females) admitted to the treatment facility during the study period. Although these individuals had experimented with many drugs, they had not smoked marijuana frequently enough to become dependent on it. They had smoked marijuana no more than 35 times in their lifetime. They smoked marijuana on average a few times a month and got drunk every 3 or 4 weeks. Use of other intoxicants, such as stimulant drugs or inhalants, was infrequent, and none of the young people was dependent on opiate drugs or cocaine.

Group C was included to control for the possible confounding effects on cognitive processing and concentration ability by emotional states of fear, anxiety, or depression possibly experienced by all adolescents immediately after entry into a treatment program. Group C also controlled to some de-

gree for premorbid personality differences between youth, who do and do not abuse drugs.

STUDY DESIGN

Urine Toxicology Tests

To ensure that study subjects remained drug free during the 6-week study period, periodic urine toxicologic tests were administered. The 18 drug-abusing participants furnished urine specimens twice a week under direct supervision from the date of entry into the treatment facility until the day of the retest. Specimens were provided by the drug-free members of group B every other week. Urine specimens were analyzed for cannabinoids and for other drugs within 7 days after collection by a licensed laboratory technologist using the Enzyme Multiplied Immunoassay Technique instrument, Syva Co, Palo Alto, Calif.¹⁹

Neuropsychological Test Battery

A battery of seven neuropsychological tests (Table 1) was administered to study subjects by one of two experienced neuropsychologic technicians under the close supervision of a licensed neuropsychologist from Georgetown University Hospital. To ensure validity, the testers were initially observed by their mentor as they administered the entire battery to three pilot subjects in the same treatment facility. The testing procedure and the scoring system were matched against those of the neuropsychologist, and close agreement was reached. The tests included a full-scale score, the digit span, and verbal and performance subtests on the Wechsler Intelligence Scale for Children, as well as six standardized tests selected to measure auditory/verbal and visual/spatial immediate and short-term (delayed) memory and praxis (construction ability). To minimize interference effects, verbal and nonverbal tests were alternated. This alternation of a verbal test followed by an auditory test helped assess delayed recall in one modality before presentation of further material in that same sensory modality.

The neuropsychologic technicians were ignorant of the group to which the participants had been assigned. To further ensure objectivity, the nine adolescents in group B appeared for the assessments without their usual jewelry, in keeping with the strict rules enforced on the adolescents in the program who constituted groups A and C.

For the groups in the program (groups A and C), the first test session was conducted between day 2 and day 5 (mean, day 2.5) of the adolescent's residence in the treatment facility. We chose those days to allow for dissipation of any obvious short-term effects of cannabis intoxication on cognition and

Table 1.—Memory Tests Administered to Study Subjects

Test	Notes and Comments
Peterson-Peterson Short-Term Memory Paradigm	Four words are presented at the rate of 1 word/s. Subject is distracted by being asked to count backward by three. After a 15- or 30-s delay the subject is asked to recall all four words. The score represents the number of recalled four-word sets in 10 s.
Buschke Selective Remembering Test	A list of 12 words are presented and the subject is asked to remember as many as possible immediately, and after a 30-s delay. The 12-word list is repeated by the examiner after every unsuccessful trial up to three trials. The score is the number of trials until a perfect 12 is obtained. A good score is 12 of 12 words by the third trial. Storage, retention, and retrieval of memory are tested.
Benton Visual Retention Test	One card containing two or more simple geometric designs in close proximity is viewed for 10-s and then hidden from sight. The subject is asked to draw from memory each of a series of 10 such cards immediately after a 10-s viewing and again after a 15-min delay. A good score is at least eight figures reproduced without significant errors of omission, addition, distortion, rotation, size, or misplacement.
Wechsler Memory Scale Prose Passages	Two prose passages (each containing 22 to 24 memory units) are read and the subject is asked to recall the passages word for word—immediately, and again after a 30-min interval. The score is the number of correct responses in passages A + B divided by 2.
Complex figure drawing	The subject views a figure drawing containing 18 components. The designs are copied directly and then by recall after a 30-min delay. Either the Rey-Osterrieth or the Taylor figures are used.
Paired Associate Learning Test	The subject listens to a list of 10 paired word associates of increasing complexity. The score consists of the total number of difficult pairs recalled immediately and after a 30-min delay.

memory. For group B, the first test session was scheduled at the subject's and technician's convenience.

Six weeks after the initial assessment, each subject served as his/her own control and retook a parallel form of the same test battery. The 6-week interval was chosen by one of us (R.H.S.), who believed that memory impairment reported to him by other cannabis-dependent patients seemed to improve after the first 4 to 6 weeks of abstinence. Parallel test forms were used by the testers to control for "practice effects" from the initial test to the retest 6 weeks later. By random selection, 50% of the subjects in each group were given battery A at the initial test and battery B at follow-up, while the other half took the parallel test batteries in the reverse order.

RESULTS

Urine Toxicology Results

Eight of the 10 cannabis-dependent adolescents (group A) had cannabinoid-positive urine specimens on the day of admission to the facility and continued to have cannabinoid-positive urine specimens for a mean of 3.75 days (range, 2 to 9 days). The remaining two cannabis-dependent adolescents did not have marijuana metabolites in the initial or subsequent urine specimens. We later determined that the cutoff point (100 ng/mL) used to test for urinary cannabinoids in this study was too high and as

such could be expected to fail to detect 25% of true-positive urine specimens.²⁰ The groups receiving treatment (groups A and C) were under constant surveillance, and any use would have been noted. To the extent that undetected use occurred in group B, such use would serve to *decrease* any cognitive differences that might be observed among the groups. By the second neuropsychological test session, all subjects in group A had long since been completely detoxified. None of the individuals in group B or group C had cannabinoid-positive urine at any time during the study.

School Report Card Grades

Report cards from sixth grade were reviewed to elicit a measure of academic performance before the onset of drug use. Photocopies of report cards were received from 80% of the members of groups A and C; average grade was B-, although one subject each in those two groups had a D average. Review of comments from the teacher confirmed the absence of hyperactivity or specific learning disability. Only three report cards were received from group B members; hence, no analysis was performed for this group.

Neuropsychological Test Battery Results

The neuropsychological data were analyzed using a series of two-way multivariate repeated-measures analyses of variance, with "group" and "test session" as main effects. (Within each memory test, a number of dependent measures were available for each analysis. For example, in the Wechsler Memory Prose Passage Test, measures were available of performance from two prose passages for immediate and delayed recall conditions. These four dependent measures were analyzed as a group. For all other tests, similar multiple dependent measure analyses were performed. The use of multiple indicators helps ensure the validity of the outcomes.) These analyses enabled us to test for the significance of overall group differences and for improvements in performance between the first and second test session. They also allowed us to test for a differential "return" (improvement) between groups over trials. In testing for this anticipated improvement, we expected a significant group \times test session interaction. That is to say, we believed that members of group A would improve substantially on any of the tests from which results had initially been poor. The repeated-measures tests (use of a test-retest research design) in these analyses helped to improve the statistical robustness because each subject served as his or her own control.²¹ These analyses reduced the likelihood of type I errors in this study. The criterion for significance was established at a moderately strict level of $P < .01$.²²

Additional preliminary analyses revealed that the three study groups did not significantly differ in terms of either verbal or performance IQ scores (Wilks' lambda = .682; $F[4,46] = 2.43$; $P = .061$), or age ($F[2,24] = 2.07$; $P = .149$). The mean full-scale IQ for the 10 cannabis-dependent adolescents (group A) was 108, vs 114 for the 17 controls (groups B and C). The mean age for the 10 cannabis-dependent adolescents was 16.0 years vs 15.3 years for the 17 controls.

Table 2 summaries of the results of the multivariate analyses of variance performed on the data from the seven memory tasks. There were significant differences between groups on two

Table 2.—Multivariate Analyses for the Seven Memory Tasks*

Memory Test	Statistic, MS (Error)/P/df	Statistic, F Ratio/MS (Error)/P/df	
		Between Groups	Effects Tested Test-Retest
Digit Span and Coding	12.97/NS/2,23	3.52/29.57/NS/2,23	1.12/12.97/NS/1,23
Peterson-Peterson	3.69/NS/2,24	1.23/26.14/NS/2,24	10.39/3.69/.004/1,24
Selective Remembering	30.21/NS/2,24	.35/669.06/NS/2,24	.01/30.21/NS/1,24
Benton Visual Retention	1.67/NS/2,24	6.07/5.69/.007†/2,24	.34/1.67/NS/1,24
Wechsler Memory Passages	1.58/NS/2,23	7.04/35.31/.004†/2,23	82.78/1.58/.001†/1,23
Complex figures	22.73/NS/2,24	.45/31.29/NS/2,24	91.80/22.73/.001†/1,24
Paired Associates	.89/NS/2,23	1.32/1.81/NS/2,23	66.37/.89/.001†/1,23

*MS indicates mean square; NS, not significant.

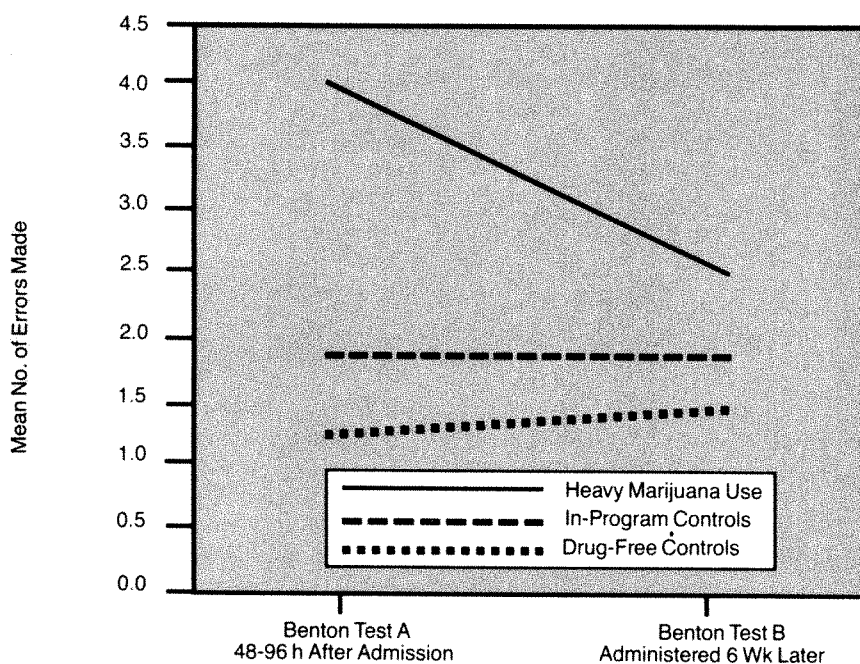
†Test remains significant at $P < .01$ when males are examined separately.

Fig 1.—Comparison of Benton Visual Retention Test scores soon after admission and 6 weeks later.

tests of short-term memory. The cannabis-dependent group (group A) committed more errors on the Benton Visual Retention Test and scored lower than the controls on the Wechsler Memory Prose Passages Test. The cannabis-dependent group did not improve statistically across time on any of the memory tests compared with the control groups.

Figure 1 presents the average number of errors for subjects within each of the three groups on the Benton Visual Retention Test, immediate recall condition. Figure 2 presents scores for the three groups on the Wechsler Memory Prose Passages Test. There is some indication of "return" for group A, the

cannabis-dependent group, in both tasks; however, as noted above, it is not large enough to provide a statistically significant repeated-measures effect.

There were substantial differences, however, in the distribution of male and female adolescents among groups. Nine of 10 subjects in group A, 6 of 9 in group B, and 3 of 8 in group C were male. Supplemental data analyses were performed to determine the effect of gender on reliability of data relating to short-term memory by using analyses of covariance, and by analyzing male adolescents separately from female adolescents (there was an insufficient number of female adolescents to per-

form the complementary analysis). Results of these analyses supported all but one of the findings. Significant group differences were maintained for both the Benton Visual Retention Test ($F[2,23]=6.39$; $P=.01$) and the Wechsler Memory Prose Passages task ($F[2,22]=6.90$; $P=.01$) when the effects of gender were statistically controlled and when males were analyzed separately ($F[2,15]=7.24$; $P=.01$ and $F[2,14]=5.93$; $P=.01$, respectively).

Pairwise comparisons among the groups in the Benton Visual Retention task showed that the cannabis-dependent group (group A) committed significantly more errors on the first testing session than group C ($F[4,21]=3.51$; $P=.02$). This difference was restricted to the pretest only, where significant differences were obtained for both immediate ($F[1,24]=12.49$; $P=.01$) and delayed ($F[1,24]=6.38$; $P=.02$) recall conditions. On the posttest, no significant differences appeared for either immediate ($F[1,24]=.42$; $P=.52$) or delayed ($F[1,24]=3.64$; $P=.07$) recall conditions. Since the likelihood of type I errors in these tests is protected by the significant overall test statistic, the criterion of significance for these contrasts was $P=.025$.²¹ Pairwise comparisons between the groups in the Wechsler Memory Prose Passages task showed that the cannabis-dependent group (group A) scored significantly lower than group C ($F[8,16]=3.91$; $P=.01$). For immediate and delayed recall, this difference appeared in both the pretest and posttest conditions. For example, using scores for the immediate recall condition for memory passage A from the test, significant differences were found between the groups both at pretest ($F[1,23]=5.47$; $P=.03$) and posttest ($F[1,23]=11.45$; $P=.01$).

COMMENT

This pilot study provided evidence of the lingering impact of heavy marijuana use on selected short-term auditory and visual memory processes. Although it was conducted in a methodologically more rigorous manner than many past efforts,^{16,17} some problems admittedly remained in the study design. Larger research efforts with at least 25 subjects in each group better matched for gender would have improved the results of our

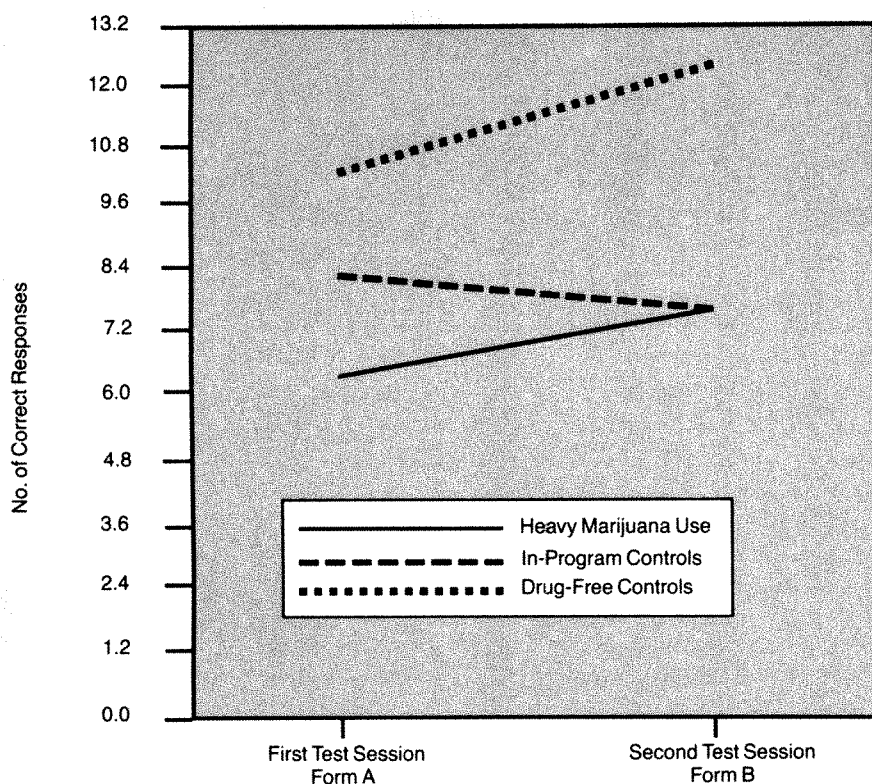


Fig 2.—Comparison of Wechsler Memory Prose Passages score soon after admission and 6 weeks later.

study. Budgetary constraints and diminished cooperativeness of the directors of the drug treatment facility obstructed the continuance of this study. We reluctantly were forced to halt the study after 27 eligible participants were enrolled.

Because the sample sizes of the groups were small, particular importance was placed on an examination of the distributions of the dependent measures. All were tested to determine if they differed significantly from normal. Three of the 21 measures used in the analyses did so; however, the particular form of the divergence from normality did not bias the result.²³ Thus, these measures were retained in their original form. Our original hypothesis was that we would demonstrate short-term memory loss in cannabis-dependent adolescents and that we would find normalization of such memory after 6 weeks. Our surprise at finding that the memory defects persisted at the 6-week retest occurred too late to modify the protocol and retest at a later date. In retrospect, additional tests of short-term memory should have been admin-

istered between 3 and 6 months after the 6-week testing session. Such repeated testing, if controlled for the "practice effect," might have demonstrated full return of any memory impairment and strengthened our hypothesis that marijuana was the main cause of the deficit. On the Wechsler Memory Prose Passages and the Benton tests, where differences between groups were observed on the initial test, there were no statistically significant "returns" in performance of the cannabis-dependent group over the 6 weeks of the study. Although Figs 1 and 2 suggest that such a return may occur, it does not appear significant ($P < .01$). The intergroup comparisons suggest that the observed differences between the cannabis-dependent group and the control groups may erode over the course of the 6 weeks in the case of the Benton Visual Retention Test; however, this finding is speculative in light of the absence of a corresponding overall significant repeated-measures effect. In the case of the Wechsler Memory Prose Passages task, significant differences were maintained between these groups through-

out the course of the study. These tasks represent two somewhat different types of information processing. The Benton Visual Retention Test requires the retention of visual information in iconic or unprocessed form over very brief periods, whereas the Wechsler Memory Prose Passages task requires the extraction of abstractions from complex stimuli (stories), encoding of these abstractions, retrieving information, and complex responding.

The failure to obtain significant differences between the cannabis-dependent group and the control group in the program may have been due to small sample sizes. Scores for the latter group were uniformly intermediate—falling between the former and the non-drug-dependent group. However, the failure to detect differences between groups A and C may also suggest that the common environments of the two groups (both appearing in the treatment program) may act to commonly alter scores on these tests.

Our current data provide little guidance on which to formulate hypotheses concerning the neurologic substrates of the observed results. Before such hypotheses may be meaningfully considered, studies should be conducted to elucidate which disruptions in what parts of the information processing system account for decreased performance. Such studies should use groups of subjects with matched gender ratios. Decreases in performance may be a function of decrements in attention, filtering, encoding, retrieval, and/or output. Isolation of the location and types of disruptions that account for the current results should, therefore, be one goal of future research in this area.

Although future research will further our understanding of the decrements we have observed, the current data have direct clinical implications. The results suggest the need to develop treatment strategies that incorporate the possibility of long-lasting cognitive deficits that may affect both performance of complex tasks and ability to learn. Results from investigations of Hawkins and coworkers²⁴ suggest that adolescents with learning disabilities are at high risk of cannabis abuse. The results reported here heighten our serious concerns about the effects of long-term

marijuana use on these already learning-impaired adolescents. For such individuals, regular use of marijuana, even to less of a degree than in our 10 study subjects, may significantly contribute to worsening school performance.

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Book Review

Management of Prader-Willi Syndrome, edited by L. R. Greenswag and R. C. Alexander, 324 pp, \$35, New York, NY, Springer-Verlag NY Inc, 1988.

This book is for all physicians, nutritionists, teachers, and other professionals who, in their work, encounter children with the Prader-Willi syndrome. The book is also an excellent resource for parents of such children.

Although one could learn how to make a diagnosis of the Prader-Willi syndrome by reading this book—Hans Zellweger has written a chapter in the book on differential diagnosis—the main thrust of the book is, as indicated in the title, the management of this difficult disorder. Medical management of hypogonadism, nutritional management of obesity, and therapeutic management of hypotonia are examples of issues pertinent to this condition that are discussed expertly and in detail.

Education, vocational training, and residential placement are other subjects covered in separate chapters. Psychological and behavioral management is discussed in one excellent chapter, but also sprinkled throughout the text is information on this crucial topic (eg, the stubbornness, food filching, and severe temper tantrums that are prominent symptoms in this disorder). The chapter on dental manifestation and management offers tips on how to deal with a child with Prader-Willi syndrome in the dental chair.

Several chapters deal with family issues. The chapter "Parents Point of View" gives practical advice, such as serving food so that portions look larger and helping children with an insatiable appetite who need less food than their

peers survive the school cafeteria. There are also good chapters on parent advocacy and networking.

Tables are used throughout this book to summarize important information. One useful table in the chapter on medical and nursing intervention lists all the major characteristics of the syndrome (as well as some minor ones like small hands and feet), their developmental sequence, and recommended intervention. Nine appendices cover a variety of subjects from syndrome-specific growth charts, food-exchange guidelines, and low-impact aerobic activity to postural control exercises (kyphoscoliosis is common in this syndrome) and summer camps.

I find little to argue with in this book. A four-page table on the nutrient content of multivitamins and mineral supplements might seem unnecessary. It is unfortunate that the old figure for recurrence rate (1.6%) has slipped into the chapter on genetics rather than the now accepted figure of 0.1%.

On the whole, however, this book is accurate, up to date, and timely. It provides much needed information not available elsewhere. *Management of Prader-Willi Syndrome* should be in the library of all professionals who minister to a child afflicted with this complex disorder.

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Acquired Immunodeficiency Syndrome Among Adolescents

Case Surveillance Profiles in New York City and the Rest of the United States

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● **Adolescents engaging in certain sexual or drug-related behavior are at risk of contracting the human immunodeficiency virus infection in endemic locales. Local and national surveillance data were analyzed to determine the characteristics of the acquired immunodeficiency syndrome (AIDS) epidemic on adolescents. Of the 605 cases of AIDS in people aged 13 to 21 years reported through 1987, 518 were males (83 from New York City [NYC], NY), and 87 were females (28 from NYC). Over half of all adolescent males with AIDS reported homosexual contact. Transfusion/blood product-related human immunodeficiency virus acquisitions (especially in males with hemophilia) represented 11% of adolescent cases from NYC (1% of NYC adults) and 22% of adolescent cases in the United States (US) outside of NYC (4% of adults in the US). Intravenous drug use was more frequently reported among adolescents with AIDS from NYC (23%) than among adolescents outside NYC (14%). In females, heterosexual transmission accounts for about half of all adolescent AIDS cases and 29% of all adult cases. Age-appropriate services and behavioral interventions are urgently needed for high-risk adolescents.**

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Reported cases of the acquired immunodeficiency syndrome (AIDS) among adolescents aged 13 to 21 years account for 1.2% of the total number of AIDS cases in the United States (US).¹ Adolescents may acquire the human immunodeficiency virus (HIV) infection in sexual or intravenous (IV) drug-related interactions with infected adults and may then serve as a conduit of infection to other adolescents.^{2,3} Adolescents at highest risk for infection are likely to be disenfranchised youths, including runaways,^{4,5} youths engaged in prostitution,⁶ incarcerated youths,^{7,8} and IV drug users.^{9,10} Early age of first intercourse^{8,11-13} and multiple sexual partners¹⁰⁻¹⁵ may increase the risk of sexually transmitted diseases, which may, in turn, facilitate HIV transmission.^{7,16-18}

The current cocaine/crack epidemic among inner-city youths is occurring in the same urban areas with the highest HIV infection prevalence.⁹ Crack use may be associated with prostitution and with disinhibited, unsafe sexual relations. Intravenous cocaine may be used.¹⁵ Male homosexual youths report a greater sense of social isolation than their adult counterparts,¹¹ and they often have older sexual partners whose seroprevalence rates are likely to be higher than those of the adolescents' peer groups in HIV-endemic areas.¹¹ Finally, many people with severe hemophilia A, including adolescents, underwent transfusions prior to the spring of 1985 with nationally marketed, HIV-infected manufactured blood products.²⁰

The risk of HIV transmission among adolescents may be especially high in New York City (NYC), NY, where seroprevalence rates are estimated to be in the 9% to 22% range for males 25 to 44

years of age living in the South Bronx.²¹ As of mid-September 1988, over 16 600 cases of AIDS had been reported in NYC (23% of the total US cases).²² Over 200 000 people in NYC are believed to be infected with HIV.^{23,24} Adolescents in NYC who engage in needle sharing, unprotected anal intercourse, or coitus with people who have engaged in these behaviors are likely to be at greater risk of HIV infection than their peers who engage in high-risk activities in regions with lower HIV prevalence.²⁵ Some insight into transmission patterns of HIV infection can be inferred from AIDS surveillance data in the adolescent age group.^{21,26,27} This study describes characteristics of reported cases of AIDS in adolescents and compares adolescents from NYC with AIDS with adults from NYC with AIDS and adolescents with AIDS in the rest of the US.

METHODS

Surveillance data for AIDS from the Centers for Disease Control (CDC), Atlanta, Ga, and the NYC Department of Health from 1979 through 1987 were analyzed based on reports received through January 19, 1988. All reported cases of AIDS in adolescents aged 13 years and older that fulfilled the CDC adult case definition of AIDS in the US²⁸ were reviewed. Surveillance programs reporting to the CDC include the 50 states, Washington, DC, Puerto Rico, and island territories in the South Pacific and the Caribbean, including Guam, American Samoa, and the US Virgin Islands. Data included in this report are from the US, excluding Puerto Rico and the territories.

Case ascertainment by the NYC Department of Health was primarily derived from four sources.²⁹ Seventy percent of the cases were reported by hospital infection control officers, while 20% were reported directly by physicians to the Department of Health.

About 5% were detected by review of death certificates, and 1% to 2% were detected by CDC from investigational drug reports and medical records.³⁰

From data reported to CDC by state health departments, categories were created to describe the presumptive origins of transmission. For this report, we further grouped cases of AIDS into one of six transmission categories: (1) male homosexual or bisexual activity, (2) male homosexual or bisexual activity and IV drug use, (3) IV drug use, (4) heterosexual activity with IV drug use or bisexual activity, (5) receipt of a transfusion of blood or blood products, and (6) other or unknown behavior. Proportional frequencies for each transmission category were compared for NYC and the US excluding NYC. The CDC surveillance system is described in more detail elsewhere.²⁰

Surveillance data were compiled by age (pediatric, under 13 years of age; adolescent, from 13 through 21 years of age; and adult, over 21 years of age), sex, and date of diagnosis. Adolescents were defined as people aged 13 to 21 years to match the American Academy of Pediatrics' definition and the administrative organization of many adolescent health care programs. Pearson's χ^2 (with Yates' continuity correction for 2×2 tables) was used to determine the significance of between-group differences.³¹ To accommodate small numbers, the very small number of male heterosexual cases were combined with the male other/unknown cases and the few female blood product-related cases were combined with female other/unknown cases in statistical comparison of NYC adolescent AIDS case proportional frequencies with those of adolescents from elsewhere in the US.

RESULTS

Characteristics of Adolescents With AIDS

As of January 19, 1988, 605 (1.2%) of 51 334 reported AIDS cases in the US were in people 13 to 21 years of age; 518 were male and 87 were female (Table). While only 3% of the nation's 13- to 21-year-olds live in NYC, 20% of all reported US AIDS cases in this age range live in NYC. Thus, NYC accounted for 6% of the total AIDS cases reported in male adolescents in the US and 32% of the total AIDS cases reported in female adolescents in the US (Table). The frequency of AIDS in the adolescent age group rises markedly with increasing age. Half of the cases in the 13- to 21-year-old age category are seen in 20- and 21-year-olds, who would be expected to represent only about 22% of the 13- to 21-year-old age group

Age Range, y	Males		Females		Total (n = 51 334)	M:F Ratio	
	NYC	US	NYC	US		NYC	US
≤12	114	307	136	205	762	0.8	1.5
13-21	83	435	28	59	605	3.0	7.4
≥22	9903	36 426	1234	2404	49 967	7.1	15.2

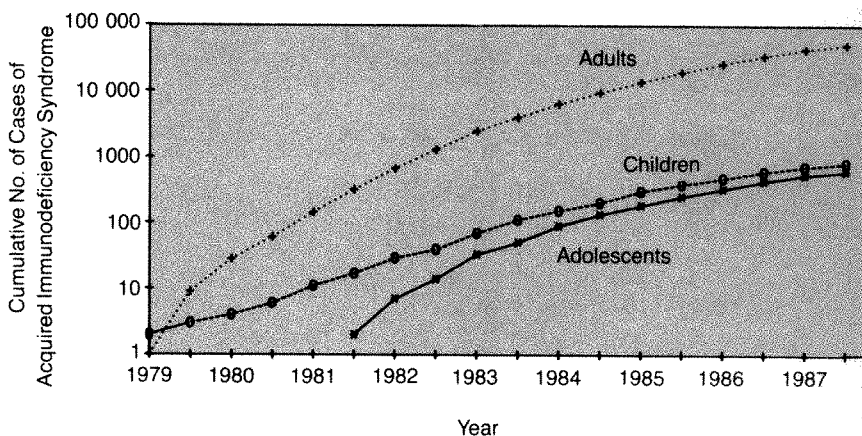


Fig 1.—Cumulative prevalence of acquired immunodeficiency syndrome cases reported to the Centers for Disease Control, Atlanta, Ga, as of January 19, 1988, by 6-month periods from 1979 to 1987 for the United States. Adults are over 21 years of age, adolescents are 13 to 21 years of age, and children are under 13 years of age.

($P < .001$). The ratio of male adolescent to female adolescent cases is 3:1 in NYC and 7:1 in the US excluding NYC, while the adult ratio is 7:1 in NYC and 15:1 in the US excluding NYC (Table).

The rate of growth in the cumulative incidence of AIDS in the US has been rapid in the first 9 years of the AIDS epidemic (Fig 1). The reported onset of the epidemic in adults and children, as documented from surveillance reports, preceded the recognition of AIDS among adolescents who were retrospectively diagnosed in 1981 (Fig 1).

Adolescents Compared With Adults

Proportional frequencies of risk behavior associated with AIDS are different in adolescent and adult cases. Both in NYC (Fig 2) and in the US excluding NYC (Fig 3), adolescents with AIDS are proportionately less likely than adults with AIDS to have acquired the infection by male homosexual activity or IV drug use. Using data from the US including NYC (data from Figs 2 and 3 combined), adolescents with AIDS are comparatively more likely to have ac-

quired the infection from transfusion of blood products (20% among all adolescent cases compared with 3% among all adult cases) or from heterosexual transmission (9% among all adolescent cases compared with 4% among all adults) ($P < .0001$).

The preponderance of transfusion/blood products-acquired AIDS is largely among males, because of the many patients with hemophilia. The heterosexual proportional differences can be attributed to differences among female patients; 47% of AIDS cases in female adolescents and 29% of AIDS cases in female adults are reportedly due to heterosexual spread, while the comparable figure among males is 2% for both adolescents and adults.

Adolescents in NYC Compared With Adolescents in the Rest of the US

Among males, a history of IV drug use, with or without a history of homosexual activity, is reported in 16% of adolescent AIDS cases in NYC compared with 4% of adolescent AIDS cases from the rest of the US. Adolescents in

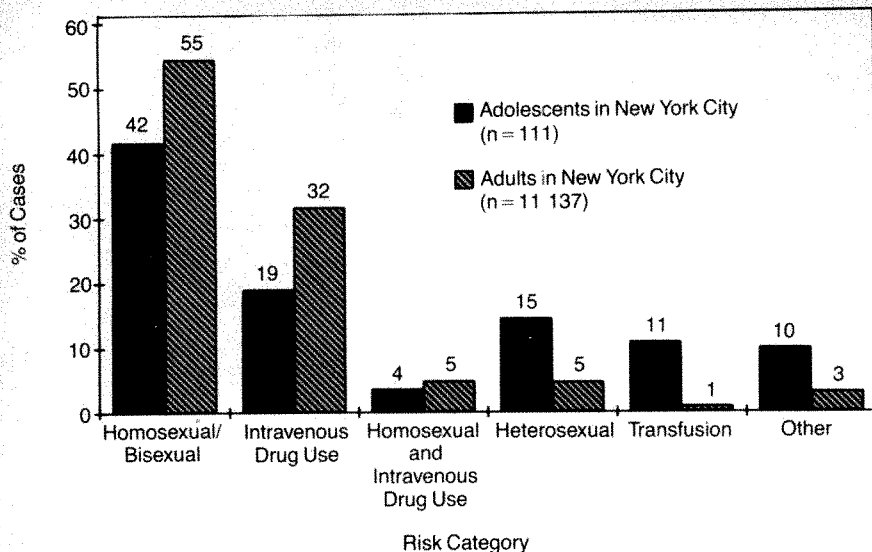


Fig 2.—Transmission profile for all adolescents aged 13 to 21 years with acquired immunodeficiency syndrome compared with adults over age 21 years with acquired immunodeficiency syndrome in New York City.

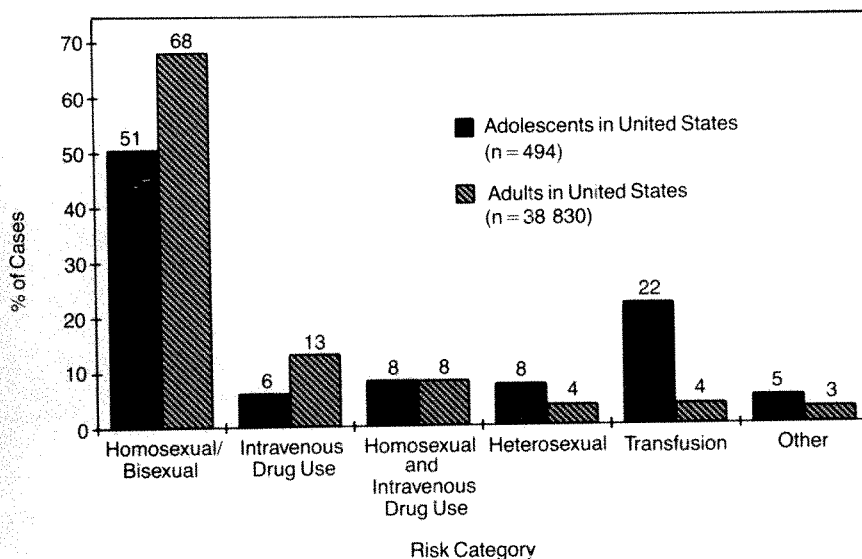


Fig 3.—Transmission profile for all adolescents aged 13 to 21 years with acquired immunodeficiency syndrome compared with adults over age 21 years with acquired immunodeficiency syndrome in the United States excluding New York City.

NYC and the US show a similar proportion of cases in males reporting homosexual/bisexual activity, from 55% to 57% of all adolescent AIDS cases (Fig 4). Transfusion-related cases are proportionately more common outside NYC. Proportional differences between cases in males in NYC and those from the rest of the US are significantly different from one another ($P < .0001$), indicating comparatively more drug use-related illness in NYC.

Proportionately more AIDS cases in female adolescents are IV drug use related and heterosexually acquired in NYC reports than in those from elsewhere in the US (Fig 5) ($P = .4$). As with male adolescents, few transfusion-related cases of AIDS are noted in female adolescents from NYC compared with those cases from elsewhere in the US. Overall differences between AIDS cases in female adolescents in NYC and in the rest of the US are not significant,

but the number of reported cases for female adolescents is small (Table).

COMMENT

Based on its population compared with the rest of the US, NYC accounts for more than six times the number of adolescent AIDS cases that would be expected if rates of AIDS were equal nationwide. Since characteristics of the epidemic differ for adolescents compared with adults, service needs are also likely to differ. For example, among adolescents with AIDS, there is a higher proportion of females than among adults with AIDS, both in NYC and in the rest of the US (Table). Since drug-related and sexually acquired cases of AIDS are proportionately more common among adolescents in NYC than elsewhere in the US, they are of special concern to health workers in NYC. The transfusion/blood product data do not suggest that the larger proportion of transfusion/blood product recipients among adolescents with AIDS outside NYC is due to higher rates of seroprevalence among persons with hemophilia. Rather, as infection rates among people with severe hemophilia A are quite similar nationwide,²⁰ people with hemophilia are a smaller proportion of the total AIDS cases in NYC than they are elsewhere in the US.

Several screening programs and seroprevalence studies have included adolescents. About 60 000 entrants, aged 16 to 21 years, to the residential training program of the Job Corps are being tested for HIV antibodies yearly.²⁰ Among these disadvantaged youth, 0.33% of the first 25 000 screened were HIV seropositive.²⁰ Military recruit applicants screened from October 1985 to July 1986 had a 0.4% seroprevalence rate in people aged 17 to 21 years.²² It is unlikely that adolescents seeking to enter the military represent youths currently at highest risk. Nevertheless, the rate ratios for HIV seroprevalence among male adolescents (13/4734, 0.3%) and female adolescents (4/854, 0.5%) reveal a relative female excess in the 17- to 21-year-old age group.²² Hence, this proportional excess risk for female adolescents compared with adults is apparent whether we are considering male-to-female ratios of reported AIDS cases, as described in the present report, or rate ratios of HIV positivity by

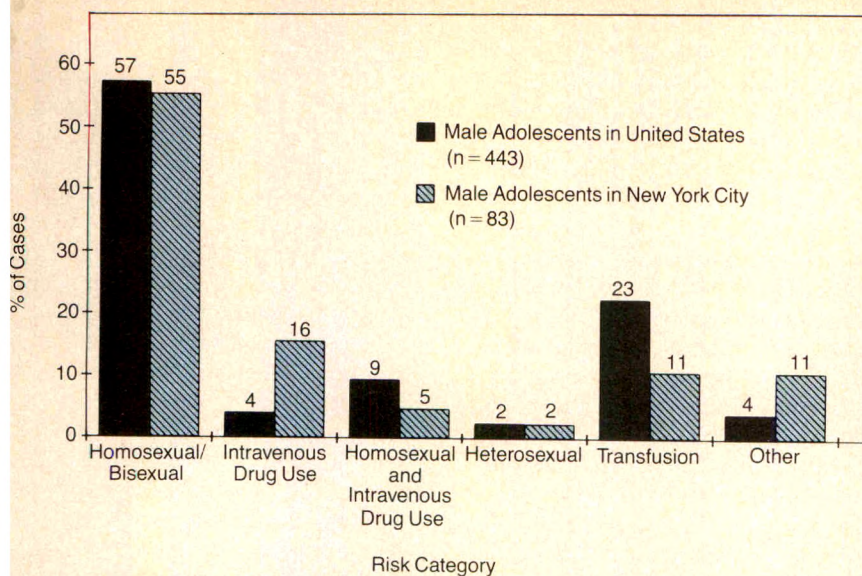


Fig 4. — Transmission profile for male adolescents aged 13 to 21 years with acquired immunodeficiency syndrome in New York City and the United States excluding New York City.

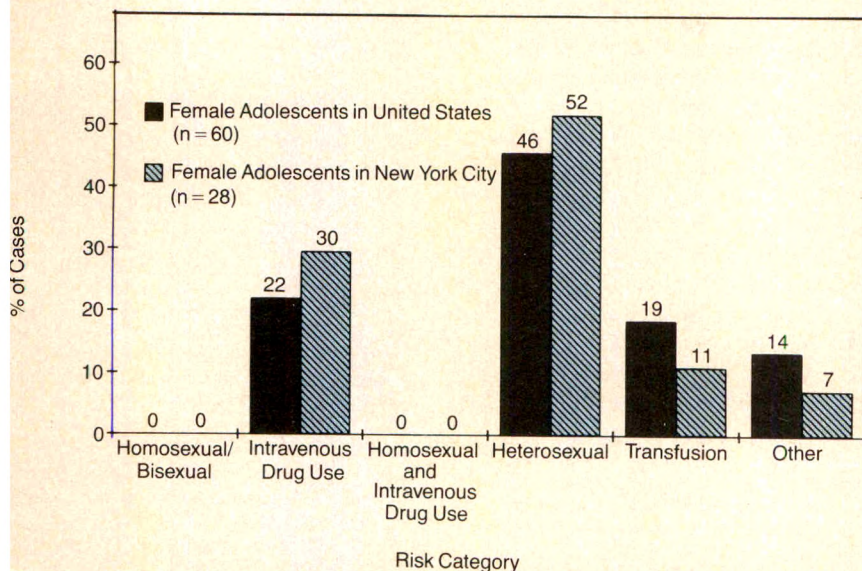


Fig 5. — Transmission profile for female adolescents aged 13 to 21 years with acquired immunodeficiency syndrome in New York City and the United States excluding New York City.

ex among military recruits. Human immunodeficiency virus seroprevalence among adolescents and young adults in NYC is the highest in the country among military recruit applicants.³³

A potential limitation in current surveillance data is underreporting of AIDS cases, particularly in low-prevalence groups or regions.³⁴ In NYC, case reporting is thought to be quite complete.^{29,30} Hence, unknown bias may enter national data that are based on a mix

of states, some of which have especially active AIDS case surveillance systems. The adolescents at highest risk often receive inadequate medical care and may be easily missed in case reporting for a number of conditions. Many of these youths may die from accidents, homicide, or suicide, which are the leading causes of death in this age group.³⁵ These competing causes of death and the inability of the current health care system to reach disenfranchised youth

may be contributing to an underestimation of adolescent AIDS cases. Given the much smaller number of cases overall among adolescents, such an undercounting, if it is occurring, would distort surveillance data far more than it would in the much larger adult case group.

Since only HIV-infected adolescents with rapid onset of AIDS³⁶ or those infected in their early teens will actually manifest signs or symptoms of AIDS by age 21 years, case reports of AIDS will inevitably underestimate the extent of the HIV epidemic among adolescents. Given the long latency of HIV infections, especially well documented among people who received transfusions on known dates,³⁷ relatively few infected adolescents will develop AIDS while still in the adolescent age group.

Higher rates of gonorrhea, syphilis, and hospitalization for pelvic inflammatory disease have been documented for sexually active adolescents than for sexually active adults.^{16,38} These differences may be due, in part, to physiologic or immunologic differences that occur during puberty which could facilitate the acquisition or spread of sexually transmitted diseases.^{16,38} It is possible that adolescents also have an increased risk of sexual transmission of HIV through the same unknown mechanisms.

A number of behavioral features related to adolescent sexuality are likely to increase the risk of HIV infection.^{2,3,7} The average age of first intercourse is 16 years in the US, though some subgroups (such as incarcerated youths) have a mean age of first intercourse as low as 12 years for both boys and girls.^{8,12,13} A substantial proportion of sexually active teenagers may have multiple sexual partners, with 41% of male adolescents and 23% of female adolescents reporting 17 or more sexual partners by age 19 years in one representative national sample.¹² In addition, female adolescents tend to have sexual partners who are, on average, 2 to 3 years older than they are.¹²

Male homosexual adolescents who have had intercourse report, on average, 7 partners by age 19 years.¹¹ The average age of their sexual partners is 7 years older than their own.¹¹ These factors may facilitate HIV sexual transmission from older infected persons to youth. High rates of unintended adolescent pregnancy continue in the 1980s,

particular among younger adolescents.¹³ Vertical transmission from an HIV-infected adolescent mother to her newborn offspring can occur.³⁸ Condom use is currently neither a popular nor a consistently used form of contraception among adolescents.^{13,14,40}

Reported drug use among a representative sample of high school seniors in the US from 1975 to 1986 reveals US rates to be the highest among the world's industrialized countries.⁴¹ While some decline in overall drug use is noted since the early 1980s, cocaine use among adolescents has remained relatively stable from 1979 to 1986. Current users, defined as people who used cocaine in any form in the preceding 30 days, represented 1.9% of seniors in the nationwide sample in 1975, 5.2% in 1980, and 6.7% in 1985,⁴¹ but fell to 4.3% in 1987 (Lloyd D. Johnston, PhD, Jerald G. Bachman, PhD, and Patrick M. O'Malley, PhD, unpublished data, January 12, 1988, University of Michigan press release). This recent trend among high school students is not particularly encouraging in relation to current patterns of reported adolescent AIDS cases.

In many inner-city neighborhoods high rates of crack use are continuing to rise.¹⁹ The substantial addictive potential of cocaine, especially in the form of crack,¹⁹ is likely to augment the risk of HIV transmission among adolescents in the inner-city neighborhoods of highest

HIV seroprevalence both by the practice of female and male prostitution to pay for or secure drugs and by possibly increasing IV drug use.^{9,17}

In addition, youth from minority backgrounds surveyed in San Francisco, Calif, and NYC have a poor fund of knowledge regarding the risk and prevention of AIDS.^{42,43} Expansion of drug prevention programs targeted toward teens and preteens, improved inner-city schools, more extensive youth job training programs, readily accessible adolescent health services focused on sexually transmitted diseases and birth control, and school-based sexual education with explicit AIDS-prevention training are all desirable.^{2,3,44} Education and training for AIDS prevention, screening and treatment programs for sexually transmitted diseases, and drug abuse prevention and treatment programs are the available means to reduce HIV transmission in the absence of a vaccine or adequate chemotherapy.^{45,46}

Given the growing number of AIDS cases among adolescents and young adults (Fig 1) and the long latency period from HIV infection to the onset of AIDS,^{36,37} seroprevalence studies are needed to measure the degree of HIV penetration into the adolescent age group. From previous experience with drug use and sexually transmitted diseases among adolescents, the spread of HIV infection is a major concern in this age group, particularly in areas of high

viral prevalence like NYC. Since adolescents are not a population with extensive experience in or resources for advocacy, community action, or self-help, it is particularly important that preventive, medical, and social services be designed by the public and private sectors to attract and retain youth. Strategies in risk reduction successfully developed among well-educated homosexual men with good peer support networks⁴⁶ may not be applicable to many adolescents at high risk.

There exists an urgent need for successful prevention and treatment models that will require community and school-based outreach and broad collaboration with those inner-city groups that have demonstrated an ability to communicate with disenfranchised youth. In the absence of a national effort to minimize the spread of HIV infection among vulnerable youth, particularly in the inner cities, the epidemic will likely expand within this age group.

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D. M. Becker; H. F. Conner; H. R. Waranch; F. Stillman; L. Pennington; P. S. J. Lees; F. Oski (*JAMA.* 1989;262:799)

Academic Medicine as a Public Trust

S. A. Schroeder; J. S. Zones; J. A. Showstack (*JAMA.* 1989;262:803)

Septic Arthritis in Children With Hemophilia

Alberto S. Pappo, MD; George R. Buchanan, MD; Andrea Johnson, MSN, PNP

• Four of the 139 children with hemophilia followed up at our center have developed septic arthritis during the past 6 years (2.9% incidence). Two infections were caused by *Streptococcus pneumoniae* and one each by *Staphylococcus aureus* and *Haemophilus influenzae* type B. Common features at time of presentation included fever and a 2- to 7-day history of joint pain and swelling unresponsive to factor replacement infusions. Since three of the patients were human immunodeficiency virus seropositive, we propose that human immunodeficiency virus infection may be responsible for the disproportionately high number of cases of septic arthritis observed in our patient population.

(AJDC. 1989;143:1226-1228)

Infectious arthritis in children with hemophilia has been reported only rarely,¹⁻⁵ and just recently has it been suggested that joint infection is more prevalent among hemophiliacs than in the general population.¹ During the past 6 years, we have identified four cases of septic arthritis among hemophiliacs followed up in our center. During our review of the clinical and laboratory features of this complication, it became apparent that immunosuppression secondary to human immunodeficiency virus (HIV) may play an important role in its pathogenesis.

PATIENTS AND METHODS

Retrospective review of the records of 139 children with hemophilia followed up at our institution between January 1983 and January 1989 indicated that there were 4 cases of septic arthritis (2.9% incidence). Three of these patients presented during the past 2 years (January 1987 to January 1989). The

salient clinical and laboratory features of these 4 patients are summarized below and in Table 1.

Clinical Characteristics

The patients ranged in age from 7 months to 13 years. All had moderately severe or severe factor VIII deficiency (factor VIII level, <5 U/dL). Presenting features common to all four children included fever (temperature $>38^{\circ}\text{C}$) and persistent swelling and pain despite appropriate factor replacement for an apparent hemarthrosis. The duration of symptoms prior to admission ranged from 2 to 7 days. All patients received factor VIII concentrate during this period; the total number of infusions ranged from two to eight. On physical examination, only one patient was described as appearing ill. None of the children had other obvious sites of infection at the time of admission; however, three of them developed this complication in a joint previously affected by recurrent bleeding ("target" joint).

Laboratory Features

All four patients presented with anemia. In two of the four patients, the hemoglobin value was lower than the usual baseline level (Table 1). The white blood cell count ranged from $4.8 \times 10^9/\text{L}$ to $12 \times 10^9/\text{L}$, with only two patients displaying a marked left shift (band leukocyte count $>0.5 \times 10^9/\text{L}$) in the differential cell count. Platelet counts were normal or slightly elevated in all four children. An elevated erythrocyte sedimentation rate (81 to 135 mm/h by Westergren method) was documented in each patient. The joint fluid was described as purulent in one patient and serosanguineous in two. Cell count and Gram's stain of the joint fluid was obtained in only two patients. Both samples had increased numbers of white blood cells ($96.8 \times 10^6/\text{L}$ and $357 \times 10^6/\text{L}$); in one patient, bacteria were demonstrated by Gram's stain. All four patients had a positive blood culture, with the same organism isolated from the diseased joint: *Streptococcus pneumoniae* in two patients, *Staphylococcus aureus* in one patient, and β -lactamase-negative *Haemophilus influenzae* type B in the other. Three of the patients were HIV-antibody positive by both enzyme-linked immunosorbent assay and Western blot methods⁶; the fourth was

HIV-antibody negative. Two of the three seropositive patients had CD4 (helper) lymphocyte counts of $0.61 \times 10^9/\text{L}$ and $0.55 \times 10^9/\text{L}$ at the time of presentation with septic arthritis; the third developed infectious arthritis in 1983, when quantitation of CD4 cells was not routinely performed in our center. However, in 1987 this patient's CD4 cell count was within the normal range ($0.91 \times 10^9/\text{L}$).

Hospital Course and Outcome

Initial treatment in three patients consisted of factor VIII concentrate at doses of 30 to 50 U/kg every 12 hours (with a dose given immediately prior to joint aspiration), diagnostic aspiration of the affected joint, and initiation of intravenous antibiotics. The fourth patient (patient 2) had joint aspiration after 5 days of hospitalization, since septic arthritis was not suspected initially. Surgical drainage and débridement, followed by irrigation of the affected joint, was carried out in three patients. One of the children (patient 1) required a transfusion of 3 U of packed red blood cells due to severe blood loss through a drain placed in the affected joint.

The mean hospital stay was 16.5 days (range, 13 to 25 days). One patient (patient 3) was readmitted 1 week after discharge with acute onset of pain and swelling in the previously infected joint. Although he was afebrile, he was treated for 1 additional week with immobilization, factor VIII concentrate, and antibiotics. Three of the patients had chronic damage in the involved joint prior to the infection described herein, and their limited range of motion diminished further after the episode of septic arthritis.

COMMENT

Septic arthritis appears to be an increasingly common complication in patients with hemophilia. To the best of our knowledge, this current report constitutes the largest pediatric series from a single institution. Our four patients displayed clinical features that are very similar to those described previously (Table 2). It is clear from our experience and that of others^{8,7,8} that septic arthritis must be included in the

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Table 1.—Clinical Characteristics and Human Immunodeficiency Virus (HIV) Antibody Status of Four Patients With Hemophilia and Septic Arthritis

Patient No./Age, y	Type/Severity of Hemophilia	Duration of Joint Pain and Swelling, d	Temperature on Admission, °C	Affected Joint	Hemoglobin Value on Admission, g/L	Organism	HIV Antibody Test	CD4 Cell Count, × 10 ⁶ /L
1/10	VIII/severe	2	40.4	R knee	109	<i>Streptococcus pneumoniae</i>	+	0.61
2/5	VIII/moderate	6	38.8	L knee	108	<i>Staphylococcus aureus</i>	+	0.91
3/13	VIII/moderate	7	39.1	L elbow	93	<i>S pneumoniae</i>	+	0.55
4/7, 12	VIII/moderate	4	39.2	L knee	85	<i>Haemophilus influenzae</i> type B	—	...

Table 2.—Features of Previously Reported Cases of Septic Arthritis and Hemophilia*

Source, y	Age, y	Type/Severity	Duration of Symptoms, d	Temperature, °C	Affected Joint	Organism
Miller et al, ⁵ 1972	8	VIII/...	2	...	L knee	...
Houghton, ²⁰ 1977	32	VIII/severe	2	39.4	R hip	<i>Staphylococcus aureus</i>
Rosner and Bhogal, ²¹ 1981	22	VIII/...	3	38.8	R knee	<i>S aureus</i>
Moseley et al, ²² 1981	57	VIII/severe	4	41	L knee	<i>S aureus</i>
Cobb, ²³ 1981	40	VIII/severe	7	39	Both shoulders, ankles, and R knee	<i>S aureus</i>
Wilkins and Wiedel, ¹² 1983	47	VIII/...	2	38.2	R knee	<i>S aureus</i>
Hofmann et al, ² 1984	12	VIII/severe	4	39.5	R knee	<i>Streptococcus pneumoniae</i>
Goldsmith et al, ⁸ 1984	40	VIII/severe	5	39.2	Both shoulders, ankles, and R knee	<i>S aureus</i>
Scott et al, ⁹ 1985	15	VIII/severe	6	39.9	R knee	Group B hemolytic streptococcus
Scott et al, ³ 1985	13	VIII/severe	3	38.9	R ankle	<i>S aureus</i>
Fajardo et al, ¹ 1986	9	VIII/...	3	39.9	L elbow	<i>S pneumoniae</i>
Mba and Njoku, ⁴ 1987	9	VIII/moderate	3	38	Both knees, both elbows	<i>S pneumoniae</i>
Ragni and Hanley, ¹⁸ 1989	26	VIII/severe (HIV seropositive)	2	...	Both knees	<i>S pneumoniae</i> (isolated from blood only)

*HIV indicates human immunodeficiency virus.

ifferential diagnosis of patients with hemophilia presenting with fever and a relatively prolonged (several days) history of localized joint pain and swelling refractory to appropriate doses of factor replacement. Suspicion of this entity should prompt the physician to aspirate the affected joint, and if the joint fluid is abnormal, initiate intravenous antibiotic therapy to limit the sizable morbidity associated with this complication.⁷

All of our patients presented with anemia, a finding previously described

in patients with hemophilia⁹; however, two of them had hemoglobin values that were lower than their usual measurements. In the absence of an obvious source of blood loss (eg, a large hemarthrosis), we speculated that the decline in hemoglobin in these two patients might have resulted from an acute episode of inflammation (ie, septic arthritis) that further depressed erythropoiesis.^{10,11} This phenomenon has been previously described in nonhemophiliacs with septic arthritis.¹⁰

Several authors^{3,4,12} have suggested that the localized joint infection in these patients results from a preceding episode of bacteremia. Our findings support this view, since the same organism was isolated from both the blood and joint fluid in all of our patients.

Although our numbers are small, several observations make us believe that HIV infection may have a pathophysiologic role in the development of septic arthritis in hemophilic patients. First, 3 of our 41 HIV-seropositive patients

have developed this complication (7% incidence). Second, it is well known that HIV infection causes multiple derangements in both T and B cell number and function,^{13,14} with affected individuals prone to develop serious bacterial infections due to *S pneumoniae*, *S aureus*, *Salmonella*, and *H influenzae*.¹⁴ Third, there has been a clustering of articles describing patients with hemophilia and septic arthritis between 1981 and 1985 (Table 2). Although the HIV serologic status of the patients is not mentioned in these previous reports, during this time period many patients with hemophilia receiving commercial factor concentrate were infected with HIV.¹⁵ Finally, a recent abstract and letter to the editor suggest that septic arthritis may be especially prevalent among HIV-infected hemophiliacs.^{16,17}

An interesting finding was the presence of pneumococcal arthritis in two of our HIV-seropositive patients and in three of the pediatric cases reported in the literature. This organism is an uncommon cause of infectious arthritis in nonhemophilic children older than 2 years of age.¹⁸ Although difficult to prove, the relatively high incidence of *S pneumoniae* septic arthritis in our patient population may be the result of altered immune function secondary to HIV infection.

One of our patients (patient 4) is unique in several respects. To our knowledge, he is the youngest hemophiliac described with septic arthritis and the only patient whose infecting organism was *H influenzae* type B. This association may be purely coincidental, since *H influenzae* type B is the most common cause of septic arthritis in chil-

dren less than 2 years of age.¹⁹ Yet, like the other cases reported herein, the insidious onset and failure to respond to appropriate doses of factor replacement suggested an initial episode of hemarthrosis.

In summary, within the past 6 years approximately 3% of the children with hemophilia attending our center have developed septic arthritis. We believe that all physicians caring for hemophiliacs should be aware that joint infections constitute a major disease complication. Diagnostic aspiration of an affected joint should be strongly considered in patients who have fever, persistent joint pain, and swelling despite appropriate doses of factor replacement. Based on our findings, HIV seropositive hemophilic children may be particularly susceptible to the development of septic arthritis. We encourage other centers that care for hemophilic children to review the incidence and pathophysiologic role of this complication.

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In Other AMA Journals

JAMA

Antibiotic Therapy for Cat-scratch Disease?

C. W. Bogue; J. D. Wise; G. F. Gray; K. M. Edwards (JAMA. 1989;262:813)

Remodelling the House of Academe

R. G. Petersdorf (JAMA. 1989;262:826)

Parent, Teacher, Child

A Trilateral Approach to Attention Deficit Disorder

Melvin L. Cohen, MD; Patrick C. Kelly, DO; A. W. Atkinson, MD, PhD

• We compared the effectiveness of three instruments in initially diagnosing and monitoring children with attention-deficit disorder with and without hyperactivity (ADD/H). Twenty-one children clinically assessed as having ADD/H and meeting criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*, were examined initially and after treatment with methylphenidate hydrochloride and placebo. The following instruments were used: the ADD-H Comprehensive Teacher Rating Scale, the Connors' Parent Rating Scale-Revised, and the Gordon Diagnostic System. The ADD-H Comprehensive Teacher Rating Scale initially classified 67% of the children as having ADD/H and 14% as borderline. The Connors' Parent Rating Scale-Revised identified 71% as having ADD/H, while the Gordon Diagnostic System assessed 52% as having ADD/H and 29% as borderline. With methylphenidate treatment, the mean scores on the ADD-H Comprehensive Teacher Rating Scale displayed an increase in attention span and a decrease in hyperactivity, the Connors' Parent Rating Scale-Revised showed a significant decrease in ADD/H behavior, and the Gordon Diagnostic System mean scores indicated no significant change. (AJDC. 1989;143:1229-1233)

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Many assessment instruments have been developed to aid in the diagnosis and treatment of children with attention deficit disorder with and without hyperactivity (ADD/H). Some are based on behavioral observations by parents or teachers, while others evaluate the child's performance of a given task. The *Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III)*, established operational diagnostic criteria for ADD/H¹ that allow for a comparison of available clinical tools. The purpose of this study was to compare and contrast a parent observation-dependent, a teacher observation-dependent, and a child performance-dependent instrument in the diagnosis and methylphenidate hydrochloride treatment of children with ADD/H who satisfied *DSM-III* criteria.

SUBJECTS AND METHODS Instruments Used

Connors' Parent Rating Scale-Revised (CPRS-R).—Developed by C. Keith Connors, PhD, and frequently referred to as the Connors' Parent Questionnaire, the CPRS-R is probably the most commonly used parent rating scale for ADD/H.² This 48-item instrument contains major groupings in conduct problems, learning disability, psychosomatic problems, impulsivity-hyperactivity, and anxiety. Ten of the 48 items make up a separate hyperactivity index used to rate the subjects in this study, with each question being answered "not at all," "just a little," "pretty much," or "very much." The number of points assigned for each response is 0, 1, 2, or 3, respectively. The sum of responses is obtained, with a score of 15 or greater generally accepted as a cutoff for a determination of hyperactivity.²

ADD-H Comprehensive Teacher Rating Scale (ACTeRS).—The ACTeRS was designed to be useful to clinicians for the diagnosis and monitoring of treatment effects in

children with ADD/H.³ This scale includes 24 items describing classroom behavior on four factors: attention, hyperactivity, social skills, and oppositional behavior.⁴ The items are scored on a scale of 1 (almost never) to 5 (almost always). The raw score for each factor is transferred to a profile sheet displaying a percentile score for each of the four factors. Separate profiles have been developed for boys and girls. Teacher responses on the attention and hyperactivity factors were evaluated in this study. Scores on the attention or attention and hyperactivity subscales of less than or equal to the 10th percentile were considered diagnostic of ADD/H.

Gordon Diagnostic System (GDS).—The GDS involves a computerized portable device consisting of a box with a button and video display screen that allows administration of two child performance tasks (delay and vigilance).^{5,6} The delay task requires the child to inhibit pushing the button for a non-specified period (6 seconds) to score a point seen on the video screen. This task is a measure of impulse control, and the number of appropriately inhibited responses divided by the total number of responses gives an efficiency ratio. The vigilance task requires the child to press the button every time a sequence of numbers (ie, a 1 followed by a 9) appears on the screen. This is a continuous performance task that yields totals for correct responses and the number of errors of commission (extraneous pushes). Scores on these three subtests (efficiency ratio, correct responses, and errors of commission) are rated as normal, borderline, or abnormal on the basis of normative data by age.⁷

Subjects

This study was conducted by the developmental pediatric service of a military medical center that serves the needs of over 49 000 children of active-duty and retired military service members. Subjects meeting protocol criteria were enrolled as they arrived at this clinic on open referral from parents, schools, or physicians. All patients were examined and followed up by board-certified pediatricians who had completed or were currently

enrolled in developmental pediatric fellowships. The protocol was approved by the institutional review board, and informed consent was obtained from parents and children. Twenty-six subjects between the ages of 8 and 12 years clinically diagnosed as having ADD/H who also met *DSM-III* criteria for this disorder were studied, and none of them had been previously treated with stimulant medication. Five subjects were subsequently removed from the study, and the data on the remaining 21 were used for analysis. All children were of normal intelligence (IQ, ≥ 80 by standardized testing). Three (14%) of the 21 subjects were girls, learning disabilities had been diagnosed by the school in 33% (7/21) of the sample, and 9 (43%) had repeated a grade in school. Further descriptive variables of this group are presented in more detail elsewhere.⁸

Methods

Extensive developmental, educational, behavioral, and social histories were obtained, and thorough physical and neurodevelopmental evaluations were performed. Participants were demonstrated to conform to *DSM-III* criteria by inquiry of parents, teachers, or both by means of the symptoms listed in the *DSM-III*. The children were then placed randomly in methylphenidate-placebo or placebo-methylphenidate groups in a double-blind fashion. Medication was administered twice daily (in the morning and at noon) on school days only. A fixed dose of 5 mg twice daily for children weighing less than 30 kg and 10 mg twice daily for those weighing 30 kg or more was used. Total daily dose ranged from 0.3 to 0.6 mg/kg.

The ACTeRS, CPRS-R, and GDS scores were obtained initially, 1 month later at the time of crossover, and 1 month after this at the conclusion of the study. Separate prescriptions were given to the parents and the school, with written instructions for appropriate administration. The interval between the last dose of medication and the beginning of the GDS ranged from 1 to 4 hours, with the majority of tests being administered within 2 hours of dosing. Parents were asked at crossover and at the conclusion of the study to give their opinion on whether their child was receiving active medication or placebo.

The instruments were considered in agreement with *DSM-III* criteria for diagnosing ADD/H if the following criteria were met: (1) a score of greater than or equal to 15 on the CPRS-R hyperactivity index; (2) a score of less than or equal to the 10th percentile on the ACTeRS attention subscale or attention and hyperactivity subscales together; and (3) an abnormal rating on any of three GDS subtests (efficiency ratio, correct responses, and errors of commission). Borderline ratings for the ACTeRS were considered between the 10th and 20th percentiles on the attention subscale. The GDS was viewed as borderline if one or more subtests was borderline and no subtest was abnormal.

Two 8-year-old patients were unable to complete the vigilance portion of the GDS and were eliminated from the GDS portion of the methylphenidate and placebo trials; the GDS was not obtained on one patient during the active substance trial, and the ACTeRS was not completed on one patient receiving methylphenidate and three patients receiving placebo, thus explaining numerical discrepancies in the results.

Mean scores for the sample population were calculated for the ACTeRS attention and hyperactivity subscales, the CPRS-R hyperactivity index, and the GDS efficiency ratio, correct responses, and errors of commission subtests. In cases where more than one parent completed the CPRS-R or more than one teacher responded to the ACTeRS, the mean score of respondents was used for analysis. Data were analyzed by means of analysis of variance for repeated measures, taking into account the crossover feature of this study.

Comparison of Initial Individual Performances on ACTeRS, CPRS-R, and GDS*						
Patient	ACTeRS		CPRS-R Hyperactivity Index	Delay Task Efficiency Ratio	GDS	
	Attention	Hyperactivity			Vigilance Task	
					Correct Response	Errors of Commission
1	A	A	N	N	B	N
2	N	N	A	N	A	B
3	A	A	N	B	N	B
4	N	A	A	B	A	A
5	B	A	N	N	...†	...†
6	A	B	A	A	...†	...†
7	N	A	N	N	N	N
8	A	B	N	A	B	B
9	B	B	A	N	N	A
10	A	N	A	N	A	B
11	A	B	A	N	B	A
12	A	A	A	N	A	B
13	A	N	A	N	B	B
14	A	B	A	N	A	A
15	N	A	A	N	N	N
16	A	A	A	N	B	B
17	A	A	A	B	N	A
18	A	A	A	N	N	N
19	A	B	N	N	B	N
20	A	B	A	N	N	B
21	B	A	A	N	B	A

*ACTeRS indicates ADD-H Comprehensive Teacher Rating Scale; CPRS-R, Connors' Parent Rating Scale-Revised; GDS, Gordon Diagnostic System; A, abnormal; B, borderline; and N, normal.

†Subject was unable to perform task.

RESULTS

Agreement with *DSM-III* criteria was established in 71% by the CPRS-R, 67% by the ACTeRS, and 52% by the GDS. The Table lists the results for each of the participants, displaying a wide disparity in the ratings and demonstrating at least one abnormal result in 90% (19/21) of cases by one of the three tools. Of the two children rated as normal on all three instruments, both were abnormal on the ACTeRS hyperactivity subscale, and one was unable to complete the GDS vigilance subtest. Further analysis of the initial ACTeRS results revealed that the inclusion of borderline attention ratings raised the sensitivity of the instrument to 81% and also displayed a subsample of children rated as hyperactive only. The inclusion of borderline ratings on the GDS increased sensitivity to 81% against *DSM-III*. The initial results on the three instruments are displayed in Fig 1.

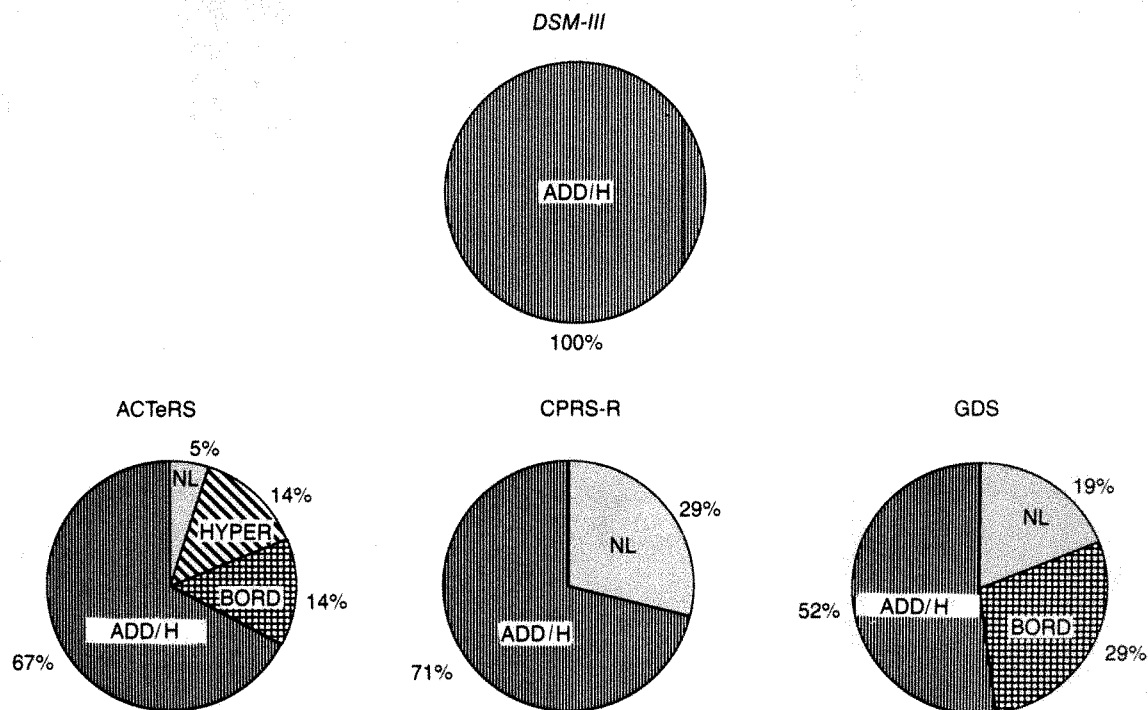
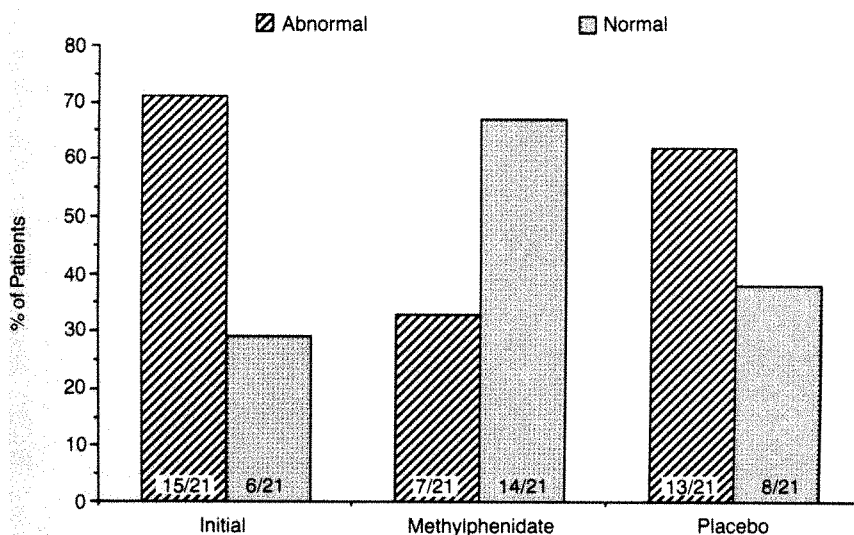


Fig 1.—Initial status of the three instruments vs the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*, criteria for a diagnosis of attention-deficit disorder with (ADD/H) and without (ADD) hyperactivity. ACTeRS indicates ADD-H Comprehensive Teacher Rating Scale; CPRS-R, Connors' Parent Rating Scale-Revised; GDS, Gordon Diagnostic System; NL, normal; HYPER, hyperactive; and BORD, borderline.

Fig 2.—The Connors' Parent Rating Scale-Revised response status initially and after administration of methylphenidate hydrochloride or placebo.



Under the influence of methylphenidate, mean scores on the ACTeRS demonstrated a marked increase (improvement) in attention ($P < .002$) and a very marked decrease (improvement) in hyperactivity ($P < .001$). The CPRS-R displayed a significant decrease (im-

provement) in hyperactive behavior ($P < .005$). The GDS mean scores on efficiency ratio, correct responses, and errors of commission demonstrated no significant change under the influence of active substance. Individual instrument classification of the subjects as

normal, abnormal, or borderline (ACTeRS and GDS) for the three trials (initial, methylphenidate, and placebo) are graphically displayed in Figs 2 through 4. A placebo effect for the ACTeRS and CPRS-R was apparent but did not reach statistical significance. Parents accurately identified methylphenidate vs placebo at crossover and again at the conclusion of the study in 76% of cases.

COMMENT

This study compared the performance of three clinical tools in the diagnosis and follow-up of medication treatment of children with ADD/H. While the *DSM-III* criteria were used as the basis of comparison, each child underwent extensive evaluation, including review of parent and teacher reports, medical history, physical and neurodevelopmental examinations, and non-standardized clinical observations, before diagnosis. Clinicians examined the children for evidence of inattention, impulsivity, and hyperactivity unexplained by apparent physical, emotional, educational, or social circumstances.

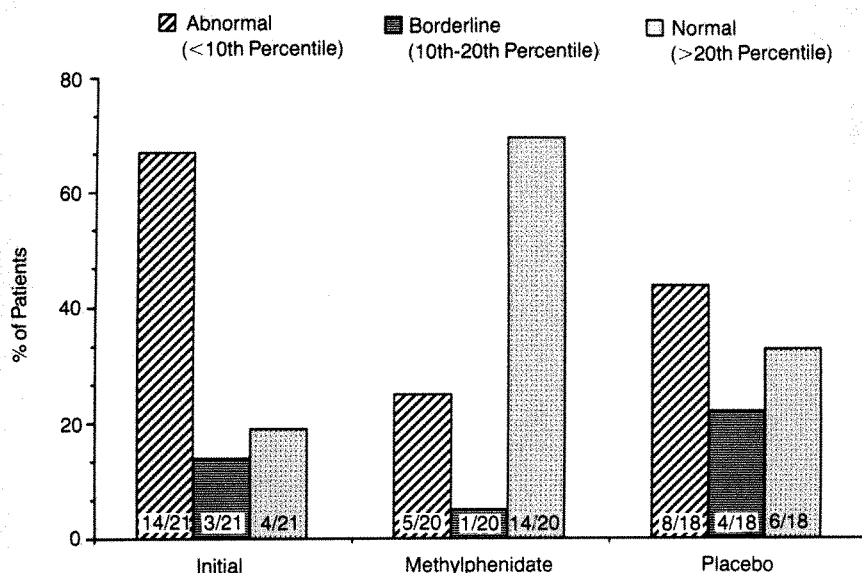


Fig 3.—The Attention-Deficit Disorder With and Without Hyperactivity Comprehensive Teacher Rating Scale response status initially and after administration of methylphenidate hydrochloride or placebo.

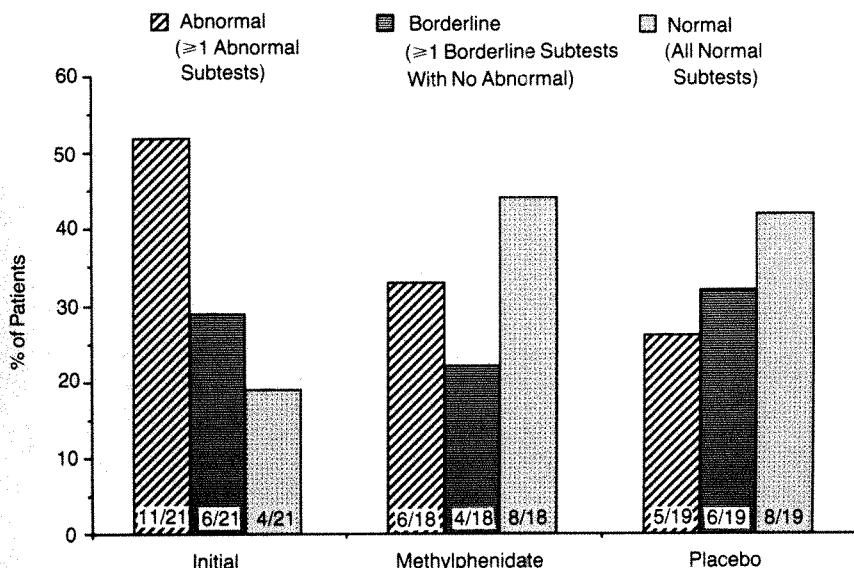


Fig 4.—The Gordon Diagnostic System response status initially and after administration of methylphenidate hydrochloride or placebo.

In addition, a clinical determination of a need for stimulant medication intervention was made in each case. Both of the above were met before enrollment in the study, and all of the subjects selected in this fashion were subsequently demonstrated to meet *DSM-III* criteria for ADD/H. Alternatively stated, the *DSM-III* criteria were 100% sensitive when compared with a clinical diagnosis of ADD/H severe enough to warrant pharmacotherapy. While recognizing a

need for operational criteria for ADD/H, we maintain that meticulous clinical evaluation should remain the major determinant of the presence of signs and symptoms of this disorder, with the studied and other instruments offering important supportive data.

Since completion of this project, a revision of the *DSM-III* has occurred, resulting in an alteration of *DSM-III* criteria for ADD/H. We regret these changes because a clear separation of

attention-deficit disorder with and without hyperactivity is no longer available. The previous edition of the *DSM-III* divided symptoms into separate criteria of inattention, impulsivity, and hyperactivity.¹ Presence of a symptom complex including inattention and impulsivity with the absence of hyperactivity allowed a diagnosis of attention deficit disorder without hyperactivity.¹ The revised *DSM-III* lists 14 symptoms, with the presence of 8 of these required for a diagnosis of the now designated attention deficit hyperactivity disorder.^{9(pp50-52)} These 14 items are based on a national field trial of criteria for disruptive behavior disorders and are arranged in descending order of discriminatory power.^{9(pp50-52)} The revised manual does offer the undefined category of undifferentiated attention deficit disorder, which includes disturbances previously designated as attention deficit disorder without hyperactivity.^{9(p86)} Our results on the ACTeRS appear to support the previously published *DSM-III* diagnostic criteria in that we found 10% (2/21) of children to be abnormal on the attention subscale with normal ratings on hyperactivity and 29% (6/21) with abnormal attention and borderline hyperactivity.

The previous edition of the *DSM-III* advised, given conflicting reports between parents and teachers, that clinicians should give greater consideration to the observations of educational professionals due to their greater familiarity with age-appropriate norms.¹ The revised edition of *DSM-III*, while eliminating this problematic recommendation, offers no advice to the clinician faced with this dilemma. Therefore, a trilateral approach using a parent observation-dependent, a teacher observation-dependent, and a child performance-dependent instrument is attractive. However, in our study the result with the child performance instrument (GDS) was abnormal in only 50% (5/10) of cases of conflicting ratings between the parent- and teacher-dependent tools. While the inclusion of borderline ratings by the GDS would raise the sensitivity of this tool and increase interinstrument agreement, further research into the establishment of a more sensitive child performance tool seems worthwhile.

The cost of the three instruments is important; the ACTeRS and CPRS-R are inexpensive when compared with the purchase price of the GDS. This factor leads us to suggest that use of the GDS may at present be most appropriate in research or large-scale screenings.

The ACTeRS was responsive to methylphenidate effect, a finding consistent with those of previous published reports.^{10,11} A placebo effect, while not reaching statistical significance, could present interpretive difficulties as the mean scores for the ACTeRS (attention and hyperactivity) improved from abnormal to borderline under the use of placebo but were in the normal range after the methylphenidate trial. Ullmann and Sleator¹¹ demonstrated a subgroup of apparent placebo responders to the ACTeRS, which could explain this finding, but the size of our sample did not allow for subgrouping of the participants. The CPRS-R was also sensitive to active substance, demonstrating an increase of greater than 1 SD. Our finding of significant improvement in the CPRS-R due to methylphenidate effect differs from that of a recently published report¹² and is interesting in that, due to the experimental design, parents had minimal contact with their children during previously suggested¹³ peak behavioral effects of the medication. We believe that this represents either a carryover effect of the medication or the influence of teacher observations on parental responses. While previous publications^{12,14} have suggested the possibility of a decline in scores on the first and second administrations of the CPRS-R,

we found no order effect on the instrument. The GDS did not demonstrate improvement under the influence of active medication. Barkley et al¹² demonstrated no effect of methylphenidate on the GDS delay or vigilance tasks when using low-dose medication. They did, however, find a statistically significant improvement in child performance on the GDS vigilance subtests when employing doses higher than those in our study. The lack of a uniform time between medication dosage and GDS administration is potentially problematic; however, the range of 1 to 4 hours is within previously determined behavioral effects of methylphenidate.¹³

While our study addressed the sensitivity of the CPRS-R, GDS, and ACTeRS vs the *DSM-III* criteria for ADD/H, it did not offer information regarding specificity of the tools, and this remains an important area of future research.

CONCLUSIONS

We conclude that the CPRS-R, ACTeRS, and GDS demonstrate utility in the diagnosis of children with ADD/H, but clinicians should avoid overreliance on any one of the individual instruments. Borderline ratings on the ACTeRS and GDS should be given clinical consideration as supportive of a diagnosis of ADD/H. The ACTeRS and CPRS-R appear helpful in monitoring the effects of treatment with methylphenidate, while the GDS does not appear sensitive to the effects of this substance at the dosages used in this study. We further offer a trilateral procedure using a parent observation, a teacher

observation, and a child performance instrument as an extremely sensible clinical approach that deserves consideration. Ideally, such a procedure would employ instruments with utility in both the diagnosis and follow-up of medication treatment of the children. As the GDS was not sensitive to the effects of methylphenidate, we cannot suggest this instrument as the child performance arm of such an approach.

While our study addressed the utility of the three instruments in the approach to children with ADD/H, it is not our intent to suggest medication as the sole variable involved in a positive outcome for those with this disorder. In our view, children with ADD/H require a multimodal approach employing selected elements of behavioral modification, family therapy, and educational adjustments in addition to indicated pharmacologic adjuncts.⁸

Despite ongoing development, revision, and refinement of instruments to assist in the diagnosis and treatment of children with ADD/H, we presently view meticulous clinical assessment and follow-up tailored to individual children as the most important factor in an appropriate approach to this multifaceted problem. The three studied clinical tools provide varying degrees of supportive data during assessment and treatment of children with ADD/H.

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School Breakfast Program and School Performance

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• To test the hypothesis that participation in the School Breakfast Program by low-income children is associated with improvements in standardized achievement test scores and in rates of absence and tardiness, children in grades 3 through 6 were studied in the Lawrence, Mass, public schools, where the School Breakfast Program was begun at the start of the second semester 1986-1987 school year. The changes in scores on a standardized achievement test and in rates of absence and tardiness before and after the implementation of the School Breakfast Program for children participating in the program were compared with those of children who also qualified but did not participate. Controlling for other factors, participation in the School Breakfast Program contributed positively to the 1987 Comprehensive Tests of Basic Skills battery total scale score and negatively to 1987 tardiness and absence rates. These findings suggest that participation in the School Breakfast Program is associated with significant improvements in academic functioning among low-income elementary school children.

(AJDC. 1989;143:1234-1239)

Disparities in educational achievement between poor and nonpoor children have long been recognized and have been the cause of grave social concern. Attempts to compensate for these disparities have resulted in large-scale social and educational efforts, such as the Head Start program, Title I com-

pensatory education, and early intervention. Nutritional problems that are more common among poor children, such as failure to thrive and iron-deficiency anemia, have been linked to academic problems.^{1,2} To date, however, there has been limited evidence supporting the role of school nutrition programs in improving the academic performance of children raised in poverty.

The School Breakfast Program (SBP) was created by Congress in 1966 (Public Law 89-642) for the primary purpose of offering a morning meal to low-income children who would otherwise have none.³ The SBP is administered nationally by the Food and Nutrition Service of the US Department of Agriculture, Washington, DC, and locally by participating school boards. Both the SBP and the National School Lunch Program offer meals to students at full price, reduced price, or free, according to uniform national eligibility criteria based on family income and size. The current Department of Agriculture criterion for eligibility for free meals is family income of 130% or less of poverty level income, and for reduced-price meals, family income of 130% to 185% of poverty level income.⁴

National survey data from 1980 show that the lunch program was available to 96% of public school children in the United States, while the breakfast program was available to only 39% of children.^{4,5} In 1986, the SBP served an average of 3.3 million meals each school day at an annual cost to the federal government of \$406 million; 84% of these meals were provided free and 4% were provided at a reduced price.⁶

Data from the National Evaluation of School Nutrition Programs (NESNP) show that the 24-hour dietary intake of children participating in the SBP is superior to that of nonparticipants who eat no alternative breakfast.⁵ It is possible that there may be other benefits associ-

ated with participation in the SBP by low-income children, such as an improvement in academic function. Such an effect is suggested by the studies of Pollitt and colleagues^{7,8} that demonstrated improved performance on morning tests of cognition by 9- to 11-year-old children following breakfast compared with their performance in the fasting state. To date, little published literature has examined the effects on academic performance of the SBP as currently administered.⁹

In August 1986, the Commonwealth of Massachusetts enacted legislation (Chapter 346, Acts of 1986) mandating the implementation of the SBP in those schools not offering the program and in which 40% or more of the school lunches were served for free or at reduced price ("severe need" schools). This circumstance enabled us to study the academic effects associated with participation in the breakfast program in a "natural experiment," in which all children in a large school district were offered the breakfast program in 1987 for the first time.

METHODS

Hypotheses

The hypotheses tested in this study were the following: (1) Low-income children who participated in the SBP for the first time would improve their academic performance, as measured by scores on standardized achievement tests, compared with their own performance when no breakfast program was available, and this improvement would be greater than any improvement shown by similar low-income children who did not participate. (2) The SBP participants would show decreased rates of absence and tardiness compared with eligible nonparticipants.

Study Site

Of the five large school districts in eastern Massachusetts implementing the SBP under the new state legislation, Lawrence was the only school system in which standardized achievement tests were administered annu-

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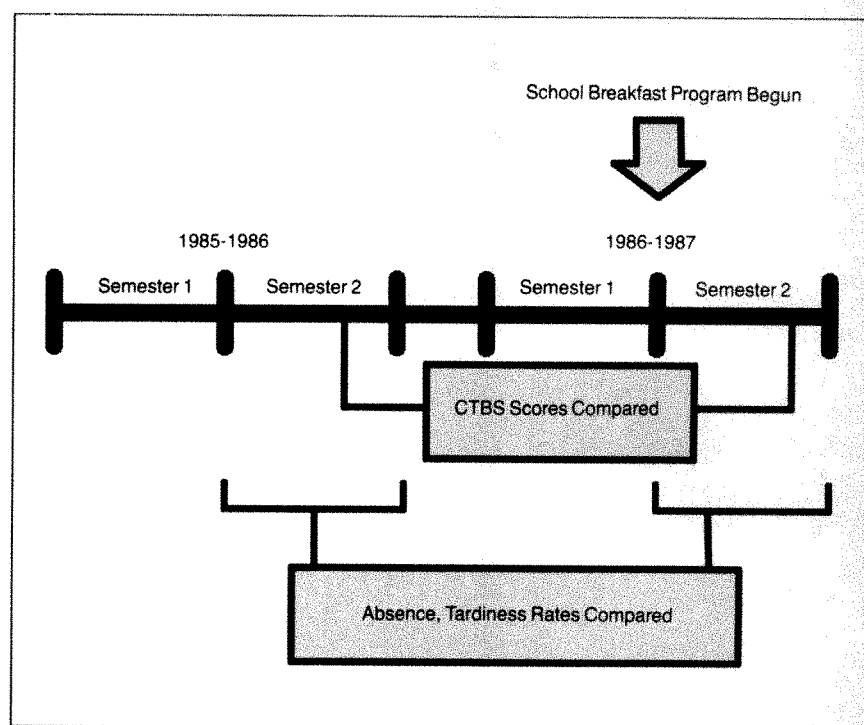
ally to all elementary grades and in which the superintendent and elementary school principals enthusiastically supported our study. Lawrence is an ethnically diverse city with a population of 63 175, of which 81% are white, 16% are Hispanic, and 2% are black. Nineteen percent of the general population and 31% of the child population live below the federal poverty level.¹⁰

In 1986, in the Lawrence Public School System, 71% of the children were low income, and thus eligible for free or reduced-price school meals. Sixty-three percent of these children were members of a minority group (58% Hispanic, 37% white non-Hispanic, 2% black, and 2% Asian); 40% of the families of these school children received Aid to Families With Dependent Children benefits (unpublished data from the Lawrence Public School System, 1986). The Comprehensive Tests of Basic Skills (CTBS), a widely used battery of standardized achievement tests, are administered annually in late April or early May to all grades, beginning in the second grade; the tests are given in the morning. The SBP was implemented in Lawrence in late January 1987, just prior to the start of the second semester of school year 1986-1987. Thus, the 1987 CTBS was administered after the SBP had been in place for 3 months.

Study Population and Data Collection

Six of Lawrence's 16 elementary schools were chosen to participate in the study. Schools were excluded from the study if they were not operating as elementary schools in 1985-1986, or if they contained two or fewer classrooms in the study grades 3 through 6. All children in grades 3 through 6 in the study schools were considered eligible for the study if (1) they qualified to receive free or reduced-price school meals; (2) they were registered in the Lawrence public schools for the second semester of both school years 1985-1986 and 1986-1987; and (3) they were not retained during the study years. Parental consent forms were sent home with all the children in the study classrooms, and those children whose parent(s) indicated on the returned forms that they declined consent were not included in the study.

To classify a child as a SBP participant or nonparticipant, attendance at the school breakfast was monitored for 1 week. Breakfast program participation was recorded on site by school personnel during the week of May 4 through 8, 1987, for which they received monetary compensation. This was the week the CTBS was administered, over the course of 3 days. Children were considered for the study only if they had been present and not tardy on 3 or more days during the sample week, according to school attendance records. They were considered SBP partici-



Study design.

pants if they attended the school breakfast on at least 60% of these days, and considered nonparticipants if they did not attend the SBP on any of these days. The remaining children were excluded from the analysis.

Demographic data were obtained from student and school registration records. Grade and age were not both included as variables, since they are so closely related; we therefore chose to include only the student's grade, which we judged to be more accurately recorded. The CTBS scores for 1986 and 1987 (scale score for battery total and language, reading, and mathematics subtests) were obtained from a printed record supplied by the CTBS scoring company, contained in the students' records. To compare the children's absence and tardiness rates before and after the implementation of the SBP, attendance and tardiness data for the spring semesters of 1986 and 1987 were collected from the central data registry of the Lawrence public schools. The study was approved by the Human Studies Committee of the Trustees of Health and Hospitals of the city of Boston.

Study Design and Statistical Methods

For each child, changes in CTBS scores were calculated by subtracting the scale scores for 1986 (prior to the SBP implementation) from the corresponding 1987 score

(after the SBP was in place). Since the SBP was implemented at the start of the second semester of school year 1986-1987, rates of absence and tardiness were compared for the second semesters of school years 1985-1986 and 1986-1987 (Figure). Absence and tardiness rates were calculated for each student by dividing the number of days the child was absent or tardy by the number of days the student was registered for school, and expressed as a percentage. Changes in absence and tardiness rates were calculated by subtracting the rate for the second semester 1985-1986 from the rate for the second semester 1986-1987.

If a child was absent or tardy for more than one fourth of either study semester, or was registered for fewer than half the total school days in session for either semester, the child was excluded from the analyses of absence and tardiness rates. One-way analysis of variance (ANOVA) was used to determine if the changes in CTBS scores, absence rates, and tardiness rates were significantly different for participants in the SBP compared with eligible nonparticipants. The ANOVA was used rather than the more familiar Student's *t* test to test for interaction effects. These two groups were also compared with regard to their 1986 (pre-SBP) CTBS scores, attendance, and tardiness using one-way ANOVA. The demographic characteristics of SBP participants and nonparticipants were compared using the χ^2 statistic.

Table 1.—Selected Sociodemographic Characteristics of School Breakfast Program (SBP) Participants vs Nonparticipants*

Variable Categories	No. (%) of Participants (n = 335)	No. (%) of Nonparticipants (n = 688)	P (χ^2 test)
Grade (n = 1023)			
Third	77 (23.0)	97 (14.1)	<.0001
Fourth	110 (32.8)	206 (29.9)	
Fifth	87 (26.0)	177 (25.7)	
Sixth	61 (18.2)	208 (30.2)	
Sex (n = 1021)			
M	171 (51.2)	347 (50.5)	.89
F	163 (48.8)	340 (49.5)	
Mean No. of children in family	3.4 (n = 331)	3.4 (n = 676)	.89
Language spoken at home (n = 993)			
English	123 (37.4)	238 (35.8)	.36
Spanish	168 (51.1)	325 (48.9)	
Spanish and English	24 (7.3)	55 (8.3)	
Other	14 (4.2)	46 (6.9)	
SBP income eligibility (n = 1023)			
Free meals	328 (97.9)	631 (91.7)	.0002
Reduced-price meals	7 (2.1)	57 (8.3)	
Ethnicity of child (n = 1012)			
White non-Hispanic	91 (27.3)	200 (29.4)	.15
Hispanic	225 (67.6)	425 (62.6)	
Other	17 (5.1)	54 (8.0)	
Classroom type (n = 1023)			
Regular	247 (73.7)	589 (85.6)	<.0001
Transitional/bilingual	81 (24.2)	96 (14.0)	
Cambodian	7 (2.1)	3 (.4)	

*Participants are defined as those children who were present and on time 3 or more days during the sample week, and who attended SBP at least 60% of the days they were present. Nonparticipants are defined as those children who were present and on time 3 or more days and who did not attend SBP on any days they were present. Sixty-nine children were absent more than 2 days during the sample week and were excluded from the analysis.

Multiple regression analysis was used to determine the contribution of independent variables, including demographic characteristics, income category, SBP participation status, and 1986 CTBS scale scores and second semester absence rates to the dependent variables. These dependent variables, or outcome measures, were defined as each child's 1987 CTBS scale scores for battery total and for subtests in language, reading, and mathematics and each child's 1987 absence and tardiness rates.

RESULTS

Study Sample and Participation

There were 1954 children in grades 3 through 6 in the study schools. Of these children, 1573 (80.5%) qualified for free or reduced-price meals. The parents of 119 (7.6%) of these children declined participation in the study. Of the 1454 children remaining, 1171 were in the Lawrence schools during both study semesters, and school records were avail-

able for a total of 1092 children. Of these children, 1023 were SBP participants or nonparticipants by our study definition; 69 children (6.3%) did not meet the definition for participant or nonparticipant and were excluded from the study sample. Three hundred thirty-five children from the study sample of 1023 (33%) were SBP participants.

Demographics of Participants and Nonparticipants

Demographic characteristics of the study sample are shown in Table 1. Participants in the SBP did not differ significantly from nonparticipants with regard to sex, number of children in the family, language spoken at home, or ethnicity. Participants were significantly more likely than nonparticipants to be in grades 3 or 4 vs grades 5 or 6, to be in transitional bilingual classes vs English-only classes, and to qualify for free

meals as opposed to reduced-price meals. For 94% of the children in the sample, the language spoken at home was either Spanish or English, and 93% of the children in the sample were either Hispanic or non-Hispanic whites.

Performance Changes for SBP Participants and Nonparticipants

Table 2 shows the mean CTBS battery total scale scores, subtest scale scores for language, reading, and mathematics, and attendance and tardiness rates for program participants and nonparticipants for 1986 (pre-SBP) and 1987 (post-SBP), and the mean change in these values. Program participants had significantly lower scores than nonparticipants in 1986 for CTBS battery total ($P < .01$), reading ($P < .05$), and mathematics ($P < .01$), and marginally lower scores for language ($P < .1$). Absence and tardiness rates for the second semester 1985-1986 (pre-SBP) did not differ between the two groups. Increases in scores from 1986 to 1987 were significantly greater for the SBP participants than nonparticipants in CTBS battery total scale score ($P < .01$), language subscore ($P < .05$), and marginally greater for mathematics ($P < .1$) and reading ($P < .1$). Tardiness rates decreased for participants and increased for nonparticipants ($P < .01$).

Independent Effect of SBP Participation on Performance

Only the children who were either Hispanic or white non-Hispanic (93% of the study sample) were included in the multiple regression analysis. Due to the high degree of collinearity (that exists when two variables vary together so closely that their independent effects cannot be distinguished) between ethnicity and language spoken at home ($r = .8$) and to the fact that virtually all the students in transitional bilingual education classes were Hispanic, only ethnicity was included in the regression model. This analysis employs casewise deletion, and thus any case with missing data for any independent variable was excluded from the analysis. Regression results are presented in Table 3.

Each coefficient represents the difference in the dependent variable that can be expected as a result of a unit change in the independent variable be-

Table 2.—Mean Test Scores and Absence and Tardiness Rates of School Breakfast Program (SBP) Participants vs Nonparticipants Before and After SBP Implementation*

Dependent Variables	1986 (Pre-SBP)			1987 (Post-SBP)			Change From 1986 to 1987		
	Participants	Nonparticipants	P of F	Participants	Nonparticipants	P of F	Participants	Nonparticipants	P of F
CTBS† battery score (n = 638)	363.10 (n = 200)	379.56 (n = 438)	.0045	411.23 (n = 200)	420.35 (n = 438)	.1018	48.13 (n = 200)	40.78 (n = 438)	.0049
CTBS math score (n = 668)	370.77 (n = 208)	384.54 (n = 460)	.0025	409.30 (n = 208)	418.27 (n = 460)	.0545	38.53 (n = 208)	33.73 (n = 460)	.0930
CTBS language score (n = 680)	420.52 (n = 205)	430.81 (n = 475)	.0580	458.25 (n = 205)	461.92 (n = 475)	.4817	37.73 (n = 205)	31.12 (n = 475)	.0238
CTBS reading score (n = 696)	386.95 (n = 206)	400.60 (n = 490)	.0141	430.43 (n = 206)	439.24 (n = 490)	.1044	43.48 (n = 206)	38.65 (n = 490)	.0977
Absence rate, % (n = 953)	5.73 (n = 311)	6.13 (n = 642)	.2812	6.23 (n = 311)	7.08 (n = 642)	.0288	-.50 (n = 311)	-.95 (n = 642)	.2738
Tardiness rate, % (n = 988)	1.53 (n = 329)	1.56 (n = 659)	.8627	.93 (n = 329)	1.83 (n = 659)	.0000	.60 (n = 329)	-.27 (n = 659)	.0014

*See Table 1 for definition of participation.

†CTBS indicates Comprehensive Tests of Basic Skills.

ng examined. Thus, the increment of 5.44 represents the expected increase in the CTBS battery total score that is associated with school breakfast participation, all other variables being held constant. School Breakfast Program participation contributed significantly to the prediction of 1987 CTBS battery total scale score ($P < .05$), and followed only grade in school and 1986 battery total scale score in the weight of its contribution. Participation contributed negatively to 1987 rates of absenteeism ($P = .05$) and tardiness ($P = .0001$).

COMMENT

In this study of the effects of SBP on school performance, we found that participation in the program by low-income children had a significant association with improvement in standardized achievement test scores and rates of absence and tardiness. Several previous controlled experimental studies, conducted in a classroom setting, suggested that there may be academic benefits associated with morning feedings¹¹⁻¹⁴; others have found no effect.¹⁵ Two experimental breakfast programs have been reported. In one, no academic benefits were found in the experimental school,¹⁶ and in the other, improvements in growth, hematocrit values, and attendance were found among children in the experimental school.¹⁷ Several non-experimental studies of the academic effects of school feeding programs have been reported as well; some have found improved academic performance,¹⁸ be-

Table 3.—Effects of Independent Variables on School Performance*						
Independent Variables	Dependent Variables					
	Battery Score 1987 (n = 540)	Language Score 1987 (n = 583)	Reading Score 1987 (n = 596)	Math Score 1987 (n = 563)	% Absence 1987 (n = 827)	% Tardiness 1987 (n = 861)
School breakfast program participation	5.44	3.61	-.53	4.50	-.71	-.83#
Grade in school	-6.01#	-1.39	-2.59	2.08	.19	.33¶
Income category	-3.06	4.19	-1.27	-1.78	-2.32¶	-.56
Children in family	-1.67	.08	-2.51¶	-1.60§	.12	.11§
Ethnicity of child	3.62	.66	7.45	3.91	-.50	-.48
Sex of child	4.89	4.79§	-1.62	9.98#	-.15	-.54¶
Absence rate 1986	-.44§	-.15	-.65	-.47§	N/A	N/A
Starting value 1986	.93#	.80#	.84#	.79#	.43#	.13¶
F of regression	279.32	172.25	193.44	135.84	31.69	8.72
Significance of F	<.00001	<.00001	<.00001	<.00001	<.00001	<.00001
Adjusted R ²	.81	.70	.72	.66	.21	.06
SE of regression	28.19	33.81	34.03	31.96	4.88	2.95

*The effect of each independent variable is measured by the unstandardized coefficient of the variable in the multiple regression analysis. Each coefficient represents the actual change in score that could be expected from a unit change in the independent variable. Because these coefficients are related to the units of measurement, their relative magnitude cannot be directly compared. Dichotomous variables were coded as follows: SBP participation; 0 = nonparticipation, 1 = participation; income category; 0 = free meals, 1 = reduced-price meals; ethnicity; 0 = Hispanic, 1 = white non-Hispanic; sex; 0 = m, 1 = f.

†See Table 1 for definition of participation.

‡These values represent the 1986 starting values for each dependent variable.

§.05 < $P \leq .10$.

||.01 < $P \leq .05$.

¶.001 $P \leq .01$.

$P \leq .001$.

havior,¹⁹ or attendance²⁰; one reported no effect on attendance.¹⁹ There have also been many anecdotal reports of improvements in school performance, tardiness, and attendance associated with the implementation of the SBP.^{6,20-24}

The academic improvements demon-

strated in this study could be due to either the immediate effects of a morning meal eaten at the start of the school day, a more long-term benefit related to improved 24-hour dietary intake, or a combination of both. If the improvement is related to the long-term effect of

improvements in dietary status, there may be even greater measurable effects for periods longer than the 3 months the program was in place in Lawrence prior to the 1987 achievement testing and the 5 months during which absence and tardiness were monitored. Recently, Benton and Roberts²⁵ showed that a vitamin-mineral supplement administered daily in school for a period of 9 months resulted in a statistically significant improvement in nonverbal intelligence test scores in a double-blind placebo-controlled trial among 12- and 13-year-old children in Britain.

The observed effect of SBP participation on achievement test scores in this study is seemingly modest. However, the national norms for the CTBS battery total scale score have an SD ranging from 41 to 50 in grades 3 through 6 (mean scale score increases each year between 12 and 43 points).²⁶ Thus, in our study, the increase in scores associated with breakfast program participation is in the range of 0.10 SD; by comparison, it is estimated that the Title I/Chapter 1 Compensatory Education Program narrowed the gap in achievement test scores between minority and nonminority students by 0.02 to 0.06 SD.²⁷ In those school districts using fixed cut points in standardized achievement test scores as criteria for promotion, score differences of this magnitude may mean the difference between promotion and retention.^{28,29}

Participation rates in the SBP in Lawrence were comparable with those found in the NESNP in 1980,⁴ in which participation rates were similarly estimated using a 5-day sample.³⁰ As in Lawrence, NESNP data showed that students tend to eat school breakfast either every day or not at all. Of those children approved for free or reduced-price meals in the NESNP sample, 21% received school breakfast on a typical school day where the program was available, compared with 33% in the Lawrence sample. In the NESNP sample, as in Lawrence, SBP participation decreased with increasing family income and increasing grade in school.

There are a number of limitations that must be taken into account in interpreting the findings of this study. This was not a controlled experiment, and thus causal inferences must be made with

caution. Since the children's participation status was determined by self-selection, it was not possible to control for some potentially confounding factors, such as motivation. The only data we were able to examine to characterize the two self-selected cohorts of breakfast program participants and nonparticipants were those available from school records and registration data.

Several variables that might be potentially confounding were therefore not examined, including family income within the broader categories of eligibility for free or reduced-price meals, educational attainment of the parents, single-parent family structure, or length of residence in the United States. In addition, we examined the grade and not the age of the children; therefore, it is possible that the age of SBP participants and nonparticipants may have differed. However, by excluding children who were retained during the study years, this possibility was reduced. While SBP participants and nonparticipants did not differ in many of the demographic characteristics studied, participants had significantly lower mean CTBS test scores in 1986 (pre-SBP).

While it is true that applying statistical tests of significance to multiple variables increases the probability of type I (false-positive) errors, it seemed useful to examine CTBS subscores as well as battery total scores and absence and tardiness rates. The consistency of the positive findings in multivariate analysis, and their agreement with the ANOVA results, suggests that while small in absolute magnitude, these are robust effects.

In examining the effect of SBP participation on CTBS scores, attendance, and tardiness, we were able to control for sex, ethnicity, grade, number of children in the family, income category, pre-SBP CTBS scores, absence rates, and tardiness rates, and still found an independent contribution of breakfast program participation to improvements in achievement test scores, absence, and tardiness. Since the 1986 CTBS scores were included as an independent variable in multiple regression analyses when determining the effect of SBP participation on 1987 scores and rates, regression to the mean could not explain the greater improvement of SBP partic-

ipants in their CTBS scores and absence and tardiness rates from 1986 to 1987. While additional data may explain a greater proportion of the variance in the outcome measures, there is no reason to suspect that a more comprehensive analysis would reveal diminished beneficial effects of SBP participation.

The findings reported here demonstrate improvements in academic performance, absenteeism, and tardiness associated with SBP participation among high-risk elementary school children living in poverty or near poverty. Further study of this important question is warranted, preferably using prospective controlled designs, and if such studies confirm these findings, it would appear that prudent public policy intended to address the educational disparity between poor and nonpoor children should include efforts to assure access to SBP for all low-income children. As advocates for the welfare of children, pediatricians should be aware of these potential benefits of the SBP for low-income children in their communities.

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Book Review

The Diagnostic Approach to Common Symptoms and Signs in Infants, Children and Adolescents, by P. S. Bellet, 502 pp with illus, \$38.50, Philadelphia, Pa, Lea & Febiger, 1989.

In this book "for medical students and physicians involved in the care of infants, children, and adolescents," Dr Bellet describes his diagnostic approach to the common signs and symptoms confronting the practitioner. His approach is logical and the format is consistent. Seventy-six signs and symptoms were selected and make up the individual chapters. Each chapter begins with a definition of the condition, which is followed by the diagnostic possibilities. Each differential diagnosis is then briefly discussed and, finally, an outline of a diagnostic approach is offered. Each chapter concludes with a bibliography.

The major strength of this book is that it is a good resource in pediatric differential diagnosis for the nonseasoned clinician. It is not meant to be a single reference source or a comprehensive text. The book is singled authored, but still is somewhat uneven in that some chapters are stronger than others. I didn't find any major omissions of either common problems or their differential diagnoses, but discussions of some of the diagnostic possibilities were rather terse.

As with any book of limited scope, one can question the emphasis of the presentation. Discussion of some chapters is divided into acute and chronic conditions, whereas other discussions are limited to acute causes.

Another question that may be raised concerns the balance of material in the book. More than 5 pages are devoted to causes of acute abdominal pain, but recurrent abdominal pain is presented in less than one page. Some chapters are very short and others are much longer (ranging from slightly more than 1 page to 18 pages). I would have defined certain clinical conditions in slightly different ways than Dr Bellet does and at times cited slightly different statistics. Quibbling aside, there were only a few statements in the book that I took issue with (eg, that a dull gray or bright red tympanic membrane is sufficient to diagnose acute otitis media).

Superficiality is the major problem with this book. However, this is only a potential liability because on many occasions the clinician would refer to this book only to provide a quick review and to make sure that all diagnostic possibilities were considered. At other times, the reader will be disappointed that the book does not go into greater depth. Although the list of diagnostic problems is adequate, the "pearls" to hone in on in the diagnoses are often excellent, and the vast majority of statements are correct, the discussions are often too abbreviated. It is also doubtful that the experienced pediatrician would find each chapter's diagnostic approach section very useful because they are quite basic and general.

How does this book compare with other books on pediatric differential diagnosis? As with the others, it has its strengths and weaknesses. By suggesting what to do after the enumeration of possibilities, it tries to go beyond simply presenting differential diagnoses of common pediatric problems and, to a degree, it succeeds. This book contains more cross-referencing than the other books with which I compared it. The advantage of this design is that it enables greater integration of the material, but the disadvantage is that it forces the reader to do more page flipping, which can be somewhat distracting. Overall, *The Diagnostic Approach* compares favorably with others, although I don't believe it is superior to them. Clinicians will find it useful. Medical students, residents, and midlevel clinicians will find it the most useful, especially if used in conjunction with a more comprehensive text.

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Professional Opportunities

FLORIDA — Seeking board-certified/board-eligible pediatrician to join busy solo pediatric practice on sunny west coast of Florida. Salaried position for one year leading to partnership. Please contact: D. French, MD, 1305-F South Fort Harrison, Clearwater, FL 34616. (813) 446-1161.

BOARD-CERTIFIED/-ELIGIBLE PEDIATRICIAN to join our 25-physician, multi-specialty group practice. All practice costs paid, full range of benefits and early partnership status. Experience our family-oriented community with its unsurpassed scenic beauty and outdoor recreational opportunities, situated midpoint between metropolitan Seattle and Vancouver, British Columbia. Contact: Shane Spray, 1400 East Kincaid Street, Mount Vernon, WA 98273. (206) 428-2524.

MASSACHUSETTS — Pediatrician, BC/BE, needed to join two others in busy private practice one hour west of Boston. Good coverage, hospital and salary. Mail CV to: Felix Perriello, MD, 114 Water Street, Milford, MA 01757. (508) 473-0231.

CALIFORNIA — PEDIATRIC INTENSIVIST to join progressive 13-bed PICU at Huntington Memorial Hospital in Pasadena, California, a major affiliate of the University of Southern California. Excellent salary, bonus and partnership opportunities. Persons with pulmonary training are encouraged to inquire. Inquiries to: Edgardo L. Arcinue, MD, Director, PICU, Huntington Memorial Hospital, 100 Congress Street, Pasadena, CA 91105. (818) 397-8688.

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THREE PEDIATRICIANS SEEKING FOURTH for growing practice in 61-physician multi-specialty group in city of 10,000, 40 miles south of Madison. Attractive salary and benefits. Contact: James Raettig, MD, The Monroe Clinic, Monroe, WI 53566. (608) 328-7214.

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MOUNTAIN STATES COMMUNITIES need pediatricians. Smaller communities with excellent incentive packages and referral bases. All close to mountain recreation. Call Rita Longino at (505) 262-1871; or send CV to: Excel of Albuquerque, 1717 Louisiana NE, Suite 218, Albuquerque, NM 87110.

Professional Opportunities

PEDIATRICIAN — Southeastern Oklahoma, 90 miles to Dallas, near beautiful Lake Texoma. Modern general acute care, 100-bed facility, opened in 1987. One other pediatrician and two OB/GYNs in this community of 14,000. This opportunity is available in a university town, offering cultural and sporting events as well as an excellent school system. Reply to: Tom Rozewicz, Medical Center of Southeastern Oklahoma, 1800 University Drive, Durant, OK 74701. (405) 924-3080.

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TEXAS — PEDIATRICIAN. A pediatrician is needed to establish practice in conjunction with the recruitment of a neonatologist, in College Station, Texas, the home of Texas A & M University. Financial assistance with possible future group association. Send your CV to: Professional Relations, Department ADC-9C, P.O. Box 1438, Louisville, KY 40201-1438.

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Professional Opportunities

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FLORIDA EAST COAST — PEDIATRICIAN. An outstanding opportunity for a BC/BE pediatrician to join one of two well-established and very busy pediatric groups located along the east coast of Florida. Attractive financial package with early partnership is offered. For further information send your CV to: John Hollander, Professional Relations, Humana Inc., Department ADC-9D, 500 West Main Street, Louisville, KY 40201-1438. Or call toll-free: (800) 626-1590.

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ALABAMA/FLORIDA AREA — Looking for security? Want to be your own boss? BC/BE pediatrician needed for a 70-bed hospital position. \$90,000 salary plus benefits. Send CV to: HQS, 6053 Tammy Drive, Alexandria, VA 22310; or call: (800) 359-1666.

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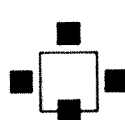
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COASTAL NORTH CAROLINA — BC/BE pediatrician sought to replace partner in four-person group. Historic town near coast. Growing practice. Immediate opening. Early partnership. Contact: Graham A. Barden, III, MD, FAAP, 707 Professional Drive, New Bern, NC 28560. (919) 633-2911.

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MASSACHUSETTS — Two BC pediatricians seeking one or two BC/BE pediatricians. Southeastern Massachusetts coastal community. Easy access to Boston and Providence. Rapidly growing practice and good hospital, recreation, spouse job opportunities, schools. Send CV: Dr. J. Conway and Dr. S. Rogers, 53 Marion Road, Wareham, MA 02571.

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UTAH — PEDIATRICIAN. An extremely busy and well-established pediatrician in Layton, Utah is now seeking an associate. This physician has two offices, one of which is located next to our 110-bed hospital. Layton, located just 20 miles north of Salt Lake City and 15 miles south of Ogden, has a service area of 140,000, 70% of whom are under the age of 35 with large families. For further information, send your CV to: Manager, Professional Relations, Humana Inc., Department ADC-9A, 500 West Main Street, Louisville, KY 40201-1438. Or call toll-free: (800) 626-1590.

NEW YORK, NEONATOLOGIST — Department of Pediatrics, State University of New York at Buffalo/Children's Hospital is seeking faculty member to join eight-member division of neonatology. Assistant or associate professor level. BC in pediatrics, IC/BE in neonatology. Division conducts NIH-sponsored laboratory research on perinatal pulmonary and circulatory physiology and clinical research in pulmonary physiology, immunology and gastroenterology, including five years experience with surfactant therapy. CV to: Frederick C. Ionn, MD, Chief, Division of Neonatology, Children's Hospital, 219 Bryant Street, Buffalo, NY 4222. Affirmative action/equal opportunity employers.

C/BE PEDIATRICIAN needed immediately to join our member pediatric department of 100-member, multi-specialty clinic with 26 satellite locations. Metropolitan population of approximately 150,000 and university affiliation. Contact: T. Mausbach, MD, akota Clinic, Ltd., P.O. Box 6001, Fargo, ND 58108. (701) 280-3346.

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Chair, Department of Pediatrics

The Allentown Hospital — Lehigh Valley Hospital Center, an 823-bed tertiary care teaching hospital in eastern Pennsylvania, is seeking a board certified pediatrician to become the first full-time Chair of its Department of Pediatrics. The successful candidate will be an accomplished clinician with the enthusiasm and vision to build a progressive, well-organized department. We will look to the Chair to create programs to assist us in providing better inpatient services, to recruit subspecialists appropriate to a service area of close to ¾ of a million people and to encourage links with educational institutions aimed at the possible development of a relationship with a tertiary pediatric program.

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Faculty Positions

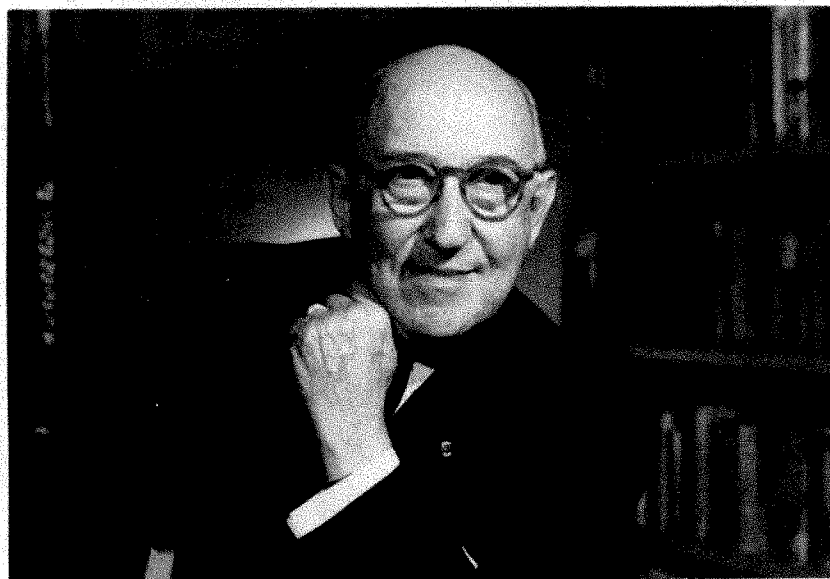
BIOSOCIAL ASPECTS OF FAMILY HEALTH: Position available for a tenure ladder faculty member in the Division of Population and Family Health, Department of Community Health Sciences. Applicants must have a PhD, MD, Dr. PH, DSW or other doctorate in field related to public health. Primary responsibilities will include participation in the teaching and research programs in family health, oriented to the USA with emphasis on child health policy and advocacy. In addition, the faculty member should have expertise in one or more of the following areas: children with special health needs, such as developmental disabilities or chronic illness and socio-political factors influencing child health programs and policy in the U.S. It is desirable that the candidate should have had experience in cross-cultural circumstances in the USA. Academic rank and salary will be based on appropriate qualifications and experience and are subject to AAU guidelines. However, assistant professor level applicants are encouraged to apply. Applicants should send cover letter and curriculum vitae to: Charlotte G. Neumann, MD, MPH, Chair Search Committee, Division of Population and Family Health, School of Public Health, University of California at Los Angeles, Los Angeles, CA 90024-1772. Applications deadline: January 15, 1990 and position would start in Fall 1990 or sooner if possible. The University of California is an affirmative action/equal opportunity employer and welcomes applications from qualified women and minority candidates.

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Application Forms For an application blank, please write to: Helene M. Cole, MD, Senior Editor, Director, Department of Editorial Affairs, Journal of the American Medical Association, 535 N. Dearborn St., Chicago, IL 60610.

Deadline For Applying Completed applications should be forwarded as soon as possible and must be received no later than January 15, 1990. The successful candidate will be notified by April 2, 1990.

AJDC

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RICHARD W. GAST
PRESIDENT

... on the consumer promotion of infant formula.

There is a development that undermines your control over the infant's diet and health, and that undermines breastfeeding—the advertisement of formulas directly to the mother through TV, magazines and mail.

On June 1, the President of the American Academy of Pediatrics sent a letter to all Fellows of the Academy reaffirming its stance against consumer advertising, and expressing concern that other formula companies might follow Nestlé/Carnation.

This concern was justified. On June 15, it was announced at a press conference that Mead Johnson/Bristol-Myers will be producing an infant formula to be sold and marketed under the Gerber label. Part of the program is a multimillion-dollar budget for advertising the formula directly to mothers via TV and print.

Speaking at the press conference, Gerber Products Division President Robert L. Johnston, Jr., said that Gerber was entering the market because it had, "identified significant changes in usage that convinced us the timing was right. ..."

"First," he said, "there is a rapid decline in breast-feeding after mothers leave the hospital." And, "... parent decision regarding baby formula brand selection has grown. ..."

The irony is inescapable and appalling. In other words, because breastfeeding is declining, more infant formulas should be promoted to the mother. In other words, because some mothers are making feeding decisions on their own, even more mothers should follow suit.

When Nestlé/Carnation entered the marketplace and, again, when Mead Johnson/Bristol-Myers joined with Gerber, we reexamined the Ross philosophy of promoting SIMILAC® Infant Formulas. The result of our deliberations was an even deeper resolve to support the doctor/patient relationship.

Our philosophy remains unchanged. Ross Laboratories has no plans to resort to direct consumer advertising for SIMILAC and our other infant formula products.

We will continue as an ally of health care professionals by supporting your prerogative to prescribe and recommend products as training and experience dictate.

We stand behind you.

Richard W. Gast





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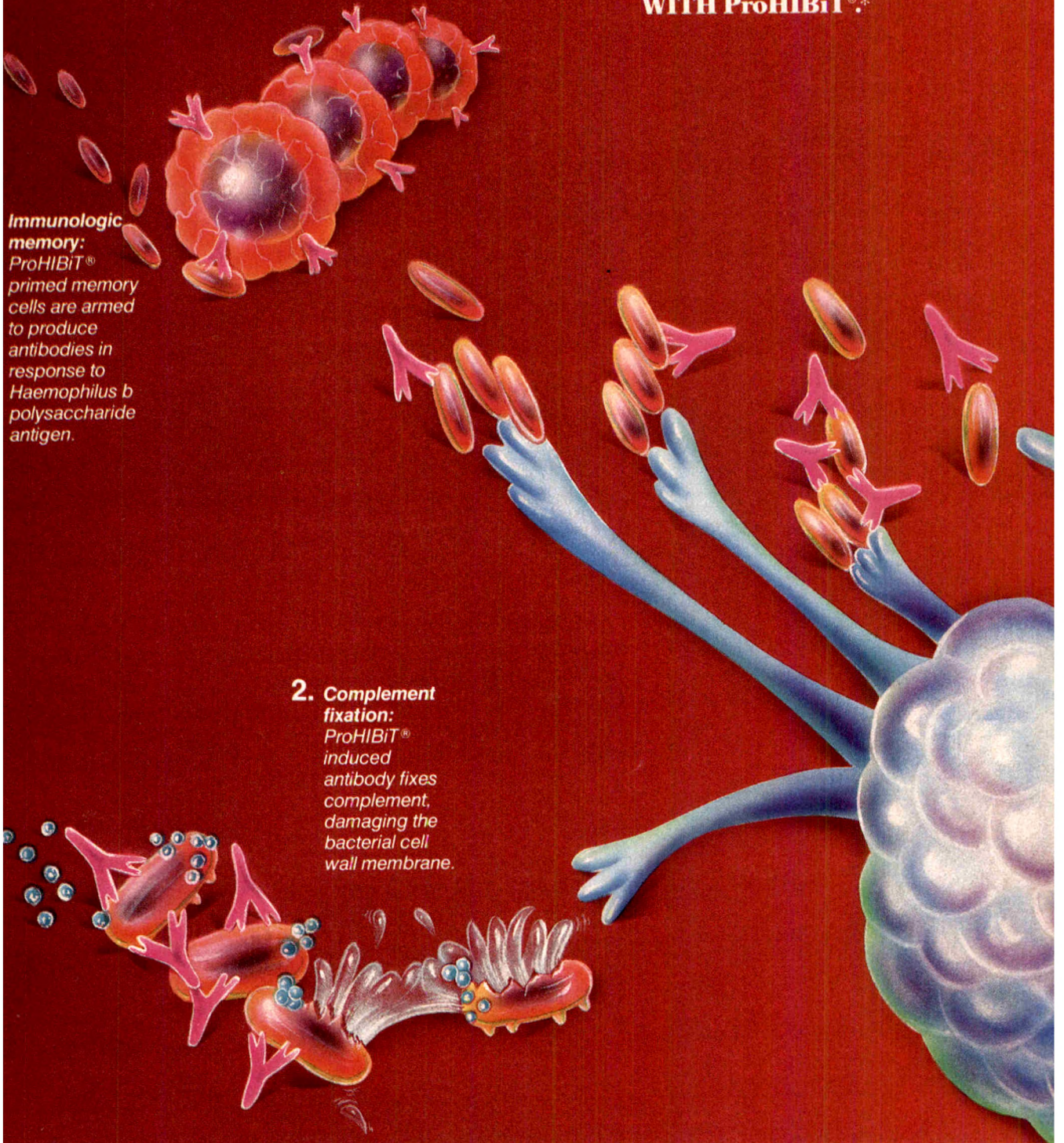
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*ProHIBiT® is currently indicated for children 18-60 months of age.

[†]Serious adverse experiences (seizures, Guillain-Barré syndrome), have been rarely reported in association with ProHIBiT® immunization.



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BRIEF SUMMARY

INDICATIONS AND USAGE

ProHIBiT is indicated for the routine immunization of children 18 months to 5 years of age against invasive diseases caused by *Haemophilus influenzae* type b. As with other vaccines, several days following administration of ProHIBiT are required for protective levels of antibody to be attained.

A booster dose of ProHIBiT is *not* required.

ProHIBiT will not protect against *Haemophilus influenzae* other than type b or other microorganisms that cause meningitis or septic disease.

No impairment of the immune response to the individual antigens was demonstrated when ProHIBiT and Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (DTP) were given at the same time at separate sites.

Because the safety and efficacy of ProHIBiT have not been established in children less than 18 months of age, ProHIBiT is not indicated for use in this age group at this time. Studies to establish the safety and efficacy of ProHIBiT in children less than 18 months of age are ongoing.

ProHIBiT IS NOT RECOMMENDED FOR USE IN CHILDREN YOUNGER THAN 18 MONTHS OF AGE.

CONTRAINDICATIONS

HYPERSENSITIVITY TO ANY COMPONENT OF THE VACCINE, INCLUDING THIMEROSAL AND DIPHTHERIA TOXOID, IS A CONTRAINDICATION TO USE OF THIS VACCINE.

WARNINGS

If ProHIBiT is used in persons with malignancies or those receiving immunosuppressive therapy or who are otherwise immunocompromised, the expected immune response may not be obtained.

As with any vaccine, ProHIBiT may not protect 100% of individuals receiving the vaccine.

PRECAUTIONS

GENERAL

As with the injection of any biological material, Epinephrine Injection (1:1000) should be available for immediate use should an anaphylactic or other allergic reaction occur.

Prior to an injection of any vaccine, all known precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible hypersensitivity to the vaccine or similar vaccines.

Any febrile illness or acute infection is reason to delay the use of ProHIBiT.

As reported with *Haemophilus b* polysaccharide vaccine, cases of *Haemophilus b* disease may occur in the week after vaccination, prior to the onset of the protective effects of the vaccine.

Special care should be taken to ensure that the injection does not enter a blood vessel.

A separate, sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another.

ALTHOUGH SOME IMMUNE RESPONSE TO THE DIPHTHERIA TOXOID COMPONENT MAY OCCUR, IMMUNIZATION WITH ProHIBiT DOES NOT SUBSTITUTE FOR ROUTINE DIPHTHERIA IMMUNIZATION.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

ProHIBiT has not been evaluated for its carcinogenic, mutagenic potential or impairment of fertility.

PREGNANCY

REPRODUCTIVE STUDIES — PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with ProHIBiT. It is also not known whether ProHIBiT can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ProHIBiT is NOT recommended for use in a pregnant woman.

ADVERSE REACTIONS

When ProHIBiT alone was given to over 1,000 adults and children, no serious adverse reactions were observed. Thrombocytopenia was seen in one adult but a causative relationship was not established.

When ProHIBiT was given with DTP and Inactivated Poliovirus Vaccine to 30,000 young infants, the rate and extent of serious adverse reactions were not different from those seen when DTP was administered alone. Allergic reactions such as urticaria were infrequently observed.

Selected adverse reactions following vaccination with ProHIBiT (without DTP) in subjects 16-24 months of age are summarized in Table.

TABLE				
Percentage of Subjects 16-24 Months of Age Developing Local Reactions or Fever to One Dose of Haemophilus b Conjugate Vaccine (Diphtheria Toxoid-Conjugate)				
	No. of Subjects*	Reaction %		
		6 Hours	24 Hours	48 Hours
Fever >38.3°C	281	1.1	2.1	1.8
Erythema	285	—	2.5	0.4
Induration	285	—	1.0	0.4
Tenderness	285	—	4.6	0.7

*Not all subjects had measurements at all time periods.

Other adverse reactions temporally associated with administration of ProHIBiT included diarrhea, vomiting, and crying and occurred at a frequency of ≤1.2%.

Adverse reactions in clinical evaluations among 689 children, 7-14 months of age, 24 hours after receiving a single dose of ProHIBiT, were observed and compared to 139 children who received a saline placebo. There were no significant differences in the reaction rates for fever, erythema, induration, and tenderness between the two groups.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for extraneous particulate matter and/or discoloration prior to administration whenever solution and container permit. If these conditions exist, vaccine should not be administered.

ProHIBiT is indicated for children 18 months to 5 years of age. The immunizing dose is a single injection of 0.5 ml given intramuscularly in the outer aspect area of the vastus lateralis (mid-thigh) or deltoid.

Each 0.5 ml dose contains 25 mcg of purified capsular polysaccharide and 18 mcg of conjugated diphtheria toxoid protein.

Before injection, the skin over the site to be injected should be cleansed with a suitable germicide. After insertion of the needle, aspirate to ensure that the needle has not entered a blood vessel.

DO NOT INJECT INTRAVENOUSLY.

HOW SUPPLIED

Vial, 1 Dose (5 per package) — Product No. 49281-541-01

Vial, 5 Dose — Product No. 49281-541-05

Vial, 10 Dose — Product No. 49281-541-10

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Store between 2°-8°C (35°-46°F). DO NOT FREEZE.

REFERENCES: 1. Data on file, Connaught Laboratories, Inc. 2. Weinberg GA, Granoff DM: Polysaccharide-protein conjugate vaccines for the prevention of *Haemophilus influenzae* type b disease. *J Pediatr* 1988;113:621-631.

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3. Title should be no more than 75 characters.

4. Authors should be limited to six, all of whom have contributed to the study and manuscript preparation, are familiar with its substance, and are able to defend its conclusions.

5. The title page should give full names, degrees, and academic affiliations of all authors, address for request of reprints, and, if the manuscript was presented at a meeting, the organization, place, and exact date on which it was read.

6. Writing style should conform to proper English usage and syntax; consult the *American Medical Association Manual of Style*, available from Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202.

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Journal articles: Scott GB, Buck BE, Leterman JG, Bloom FL, Parks WP. Acquired immunodeficiency syndrome in infants. *N Engl J Med*. 1984;310:76-81.

Books: Naeye RL. How and when does antenatal hypoxia damage fetal brains? In: Kubli F, Patel N, Schmidt W, Linderkamp O, eds. *Perinatal Events and Brain Damage in Surviving Children*. New York, NY: Springer Verlag NY Inc; 1988:83-91.

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2. **From Research to Relevance.**—PURPOSE: To focus on significant research that has a high probability of being translated into clinical usefulness.

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4. **Sports Medicine.**—PURPOSE: To provide current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention, diagnosis, and treatment of sports-related illnesses and injuries.

5. **Picture of the Month.**—Submissions should be sent directly to Murray Feingold, MD, National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135, and should conform to the format for original articles in terms of the text, references, and illustrations.

6. **Radiological Case of the Month.**—Submissions should be sent directly to Beverly P. Wood, MD, University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Submissions should conform to the format for original articles in terms of the text, references, and illustrations.

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This department of AJDC is reserved for comment, criticism, observation, and discussion of "issues of current concern and importance for children's health." The Editor encourages our readers to express themselves on a variety of topics and issues. Further, we encourage the submission of unique and brief clinical and scientific observations that do not fulfill the criteria for original articles.

Stress Experienced During Pediatric Residency Training Program

Sir—I write to laud the articles by Hoekelman¹ and Cohen and colleagues² in the February 1989 issue of *AJDC*. In looking at the balance between the financial needs of young people in pediatric training and the financial distress that institutions increasingly are incurring and are going to incur to an even greater degree, one wonders whether, in addition to some of the solutions suggested by the above authors, pediatric residency training should be changed, both at the training program level and at the American board level.

Of the total 3 years in pediatric residency at our institution, 3 months are spent on vacation and 6 months are spent in "electives." Of these electives, one is psychosocial and of definitive value in future practice. On the other electives, the resident acts as a junior fellow, by and large, doing the initial consultation on the patient for the fellow and then trailing the fellow and then the attending staff around the institution. The resident is seeing the same patients that he or she would have seen if carrying out patient care duties in the institution and, indeed, is seeing the same fellows or faculty that he or she sees on the pediatric electives. Despite this and despite the problems with stress during training programs and the need for what Cohen and colleagues call "humane and flexible training programs," the Accreditation Council for Graduate Medical Education (ACGME) requires a certain number of rotations in subspecialties accredited by the council for a residency program to be accredited and, indeed, for the resident to experience before he or she graduates.

There is a certain self-serving cravenness in this whole business. I seriously doubt that residents go into gastroenterology, hematology, or car-

diology because of a 1-month elective. I wish that there were ways to prove this, but in the climate of decreasing dollars, increasing stress, and problems with house staff training, I wish that ACGME and all of the training program directors would look carefully at the value and need for electives of any kind. Eliminating such electives would have to be done across the board in every program, ie, each program would have to require that there be no electives, or the programs could not be competitive. If that were done and residents were allotted to programs based on pediatrics and the pediatric subspecialties on ward rotations and in the outpatient department, I think that there would be time to both reduce the stress and make the programs more flexible to meet the ultimate goals of residency training. Personally, I think that residents could achieve staff role models much better from a continuous staff ward rotation than they presently achieve from what are often very ill-defined elective rotations.

I suggest this as one way to look at the entire problem of stress during residency training programs vs dollars required to pay residents to complete 3 years of pediatric training.

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Use of Intravenous Immunoglobulin in the Treatment of Neonatal Sepsis

The mortality and morbidity associated with neonatal sepsis and meningitis remain significant despite ad-

vances in antimicrobial chemotherapy and supportive care. Recent studies have shown that administration of a specific antibody in conjunction with antibiotics may improve the outcome of neonates with sepsis. For example, Shigeoka et al¹ showed that infants infected with group B streptococci and transfused with whole blood containing specific opsonic antibody had significantly improved survival compared with infants receiving blood lacking antibody to the infected strains. The feasibility of this combined immunotherapy and antimicrobial chemotherapy has been aided by the availability of safe preparations of human intravenous immunoglobulin (IVIG).

In contrast to conventional intramuscular immune serum globulin, IVIG can be given in large quantities to patients, regardless of body size or muscle mass, thereby providing immediate high levels of specific antibody that may be of therapeutic benefit. Two prospective control studies have been published concerning the use of IVIG in the treatment of neonatal sepsis (Table). Both studies reported that treatment with IVIG and antibiotic therapy significantly improved the survival of premature infants with sepsis compared with antibiotic therapy alone.^{2,3}

Two studies were subsequently cited as an important observation for the therapeutic potential of IVIG in neonatal sepsis.⁴ However, both studies suffered from improper statistical analysis. The Student *t* test was applied in the report of Haque et al³ for calculating the difference in the outcome, and there was no mention of specific statistical methods employed in the report of Sideropoulos et al.² Similarly, both studies failed to specify whether they were testing the null hypothesis or an alternative hypothesis.

To test the null hypothesis that there is no difference between the treatment regimens, a two-tailed

Efficacy of IVIG* in the Treatment of Neonatal Sepsis				
IVIG	Mortality, No. (%) of Patients		P†	
	IVIG	No IVIG	Reported	Corrected
pH4-treated IVIG, 1 g/d for full-term infants	1/7 (14)	0/6	NS	NS
pH4-treated IVIG, 0.5 g/d for premature infants for 6 d	1/13 (8)	4/9 (44)	.04‡	.13§
Total	2/20 (10)	4/15 (27)	NS	NS
IgM-enriched IVIG, 0.25 g/kg per d for premature infants for 4 d	1/30 (3.3)	6/30 (20)	<.001	.10§

*IVIG indicates intravenous immunoglobulin.

†NS indicates not significant.

‡Statistical methods not specified.

§Two-tailed Fisher's Exact Test.

||Student's t test.

Fisher Exact Test should have been used to analyze their data. As shown in the Table, using this revised statistical analysis, both studies showed a trend but no statistically significant differences were evident between IVIG with antibiotic therapy vs antibiotics alone.

Thus, at present, the therapeutic efficacy of IVIG for neonatal sepsis is not clear. Experimental studies have revealed that IVIG plus antibiotic therapy were beneficial in rapidly clearing bacteria from the bloodstream or in improving survival in newborn rats infected with group B streptococci or *Escherichia coli*.^{5,6}

Although IVIG has been used in many infants with sepsis on a compassionate basis, further use of this form of therapy requires carefully conducted controlled studies. These studies should also provide information on many unsettled issues concerning the therapeutic use of IVIG in neonatal sepsis, such as functional activity against common neonatal pathogens, effective optimal dose, and the potential hazards with the use of higher doses.⁷ Until data from such studies demonstrate a clear-cut benefit, a widespread prescription of IVIG in the treatment of neonatal sepsis should be restrained.

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1. Shigeoka AO, Hall RT, Hill HR. Blood-transfusion in group B streptococcal sepsis. *Lancet*. 1978;1:636-638.

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Theophylline and School Performance

Sir.—In their article in the April 1989 issue of *AJDC*, Gutstadt et al¹ reported that the low scores on standardized tests of reading and mathematics obtained by their 99 patients were significantly associated with low socioeconomic status, older age, a history of continuous steroid use, and the presence of emotional and behavioral problems. With respect to the latter finding we were surprised that even though 94 of their 99 moderately to severely asthmatic patients were being treated with theophylline, the authors made no mention of a possible association between the use of theophylline and emotional or behavioral

problems. We think that the omission of this information is important because the impression given is that the only medications among the many that these patients were taking that might have had a negative effect on their academic performance were their steroids when, in fact, theophylline's effect on their performance may have been equally significant.

Previous studies, including our own have found theophylline usage to be related to problems in visual-spatial planning, concentration, hyperactivity, depression, and anxiety. In light of such findings it seems reasonable to conclude that theophylline may be a significant determinant of school performance in children with chronic asthma as any of those identified by Gutstadt and her colleagues.

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1. Gutstadt LB, Billette JW, Mrazek DA, Fukuhara JT, LaBrecque JF, Strunk RC. Determinants of school performance in children with chronic asthma. *AJDC*. 1989;143:471-475.

In Reply.—The major finding of our study was that children with moderate to severe asthma had average to slightly above average scores for academic performance. Only a small percentage of children scored less than 1 SD below the mean for either reading or math. Having performance score at the lower end of these relative normal values did correlate with certain features of the asthma, as reiterated by DuHamel and Furukawa in their letter. A number of other variables defining asthma and its treatment, including "medication being taken at the time of the evaluation" were considered, but "did not correlate with performance" (p 474). Use of theophylline medication was recorded (Table 1, p 472) and included in the analysis. Theophylline medication may not have correlated with performance because such a high percentage (94%) of the children were using the medication. It is also possible that theophylline had an effect on performance, but was mediated through changes in behavior and was not a

parent directly. However, it seems likely that theophylline medication may not play a major role in determining academic performance in children receiving treatment with multiple medications for control of asthma, especially if there are emotional and behavioral problems that result from difficulties adjusting to the chronic illness.

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Ischemic Injury and Necrotizing Tracheobronchitis

Sir.—The article by Hanson et al¹ in the October 1988 issue of *AJDC* somewhat supported a personal belief that ischemic injury is involved in the propagation of necrotizing tracheobronchitis (NTB). However, I do not believe that their data justify a causal relationship, as the title of the article would imply. Although 58 infants with NTB had either profound hypotension or low 5-minute Apgar scores (the "ischemia" factors that differentiated them from the controls), the remaining 64 affected infants (54%) had neither of these factors. Furthermore, the authors state that their data were analyzed with "a two-tailed *t* test."¹ I suspect that they actually meant that χ^2 analysis was used. Simplistically, the *t* distribution is a method of comparing two group means, while the χ^2 statistic compares rates or frequencies of discrete findings. The *P* values presented in the tables are actually those that one would calculate using χ^2 analysis. Furthermore, since multiple comparisons of various factors are made, there is a greater likelihood of a type II error. To avoid this possibility, a number of multiple comparison procedures or adjustments are available (Bonferroni's, Tukey's, Student-Neuman-Keuls', etc). However, since the authors are individually evaluating a number of possible risk factors to ascertain causal relationships with NTB, multivariate analysis would be a better tool. One only has to examine their hypotension and 5-minute Apgar score data to realize the inadequacy of their method of analysis. One hundred twenty-two infants had NTB. Forty of these infants had 5-minute Apgar scores of 7 to 10 and subsequently developed profound hy-

potension. Of the 82 infants with lower 5-minute Apgar scores (0 to 6), only 4 developed severe hypotension. By statistically comparing these factors as the authors do their other data, $P < .0005$ is generated, and one could conclude that high 5-minute Apgar scores cause severe hypotension. Obviously, other confounding variables have to be considered. Again, multivariate analysis would represent a method of analyzing independent risk factors for causal relationships.

Hanson et al used a modified version of the scoring system of Joshi et al² to grade histologic changes. We are aware of at least four other scoring systems that attempt to quantitate airway injury.³ Our system provides a consistent, reproducible evaluation of histologic alterations.³⁻⁶ Unfortunately, the lack of a generally accepted "standard" system makes comparisons of the various studies difficult.

deLemos et al⁷ have previously postulated that NTB represents an ischemic injury related to intraluminal tracheal pressure effects on mucosal and submucosal blood flow. The concept presented by Hanson et al of tracheal perfusion pressure is a similar hypothesis. Mean airway pressure is a key part of their theory. Unfortunately, in their report they did not examine the effect of mean airway pressure on the propagation of injury. Furthermore, peak inspiratory and end-expiratory pressures were only compared in 22 of 206 infants. If such information were available, the validity of their concept could be addressed. We have also found greater damage in the upper tracheae of subjects undergoing ventilation as well as numerous "skip" areas of injury throughout the airway.⁴⁻⁶ These findings have led us to speculate that intraluminal elements that directly traumatize epithelial surfaces may also influence airway histologic changes.

Multiple mechanisms have been proposed as potential causes of the extensive damage of NTB. However, to date there have been few investigations evaluating the relative contribution of individual factors.^{4-6,8,9} Anecdotal reports or retrospective reviews can identify correlations, but they cannot establish causality. In our clinical experience, as well as in that of others,¹⁰⁻¹² NTB occurs in the most severely ill infants, frequently following a course complicated by asphyxia, hypotension, and high ventilator settings. These features led us to in-

vestigate the roles of hypotension, hypoxemia, and "high" vs "low" ventilator settings in the propagation of tracheobronchial injury during conventional mechanical ventilation.⁶ Using a newborn piglet model, we found that a combination of hypotension and hypoxemia led to more extensive histologic changes than either factor alone. Furthermore, high ventilator settings alone were not associated with more damage than low settings. Surprisingly, higher mean airway pressures did not influence the degree of changes. As Hanson et al have suggested, their theory of tracheal perfusion pressure requires further investigation.

Hanson et al are to be commended for bringing to light the very frequent pathologic finding of airway injury in infants undergoing conventional ventilation. Mammel and Boros¹³ reported that 91% of infants who die following high-frequency jet ventilation have histologic evidence of NTB at autopsy. The determinants of NTB must be identified before we can hope to modify or avoid this entity.

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Hematologic Syndrome of Growth-Retarded Infants

Sir.—The article by Philip and Tito¹ in the February 1989 issue of *AJDC* was pleasant reading. Their finding of increased nucleated red blood cell (NRBC) counts in small-for-gestational age (SGA) infants, not uncommonly associated with thrombocytopenia and leukopenia, corresponds very well with our own data.² Their hypothesis for the pathogenesis behind the increased NRBC counts (chronic hypoxemia) is also in accordance with ours. Their discussion, however, seems to me rather descriptive. They do not comment on the low platelet and leukocyte counts, and do not offer any deeper explanation for possible mechanisms.

Intrauterine growth retardation is often caused by placental malfunction, leading to long-lasting intrauterine hypoxemia and stimulation of fetal erythropoiesis. This increases output of erythroblasts to the circulation, and is successively followed by polycythemia. Air breathing after birth brings the hypoxemic condition to an end. In our patients the erythroblasts disappeared from circulation during the first week of life, while thrombocyte counts usually normalized 10 to 15 days after birth.² Experimental studies, exposing pregnant animals (mice) to persistent hypobaric hypoxemia, reproduced the growth retardation, polycythemia, and transient thrombocytopenia in the offspring.³ Studies on humoral regulation of erythropoiesis pointed to a compensated state of tissue oxygenation in most SGA infants and experimental animals because erythropoietin values were normal in the presence of an increased oxygen transport capacity (polycythemia).^{4,5} Small-for-gestational age infants had normal levels of thrombopoietin, indicating no lack of humoral drive for thrombopoiesis.⁴

In my opinion there exists a "hematologic syndrome of the SGA infant" in the early neonatal period. In its full expression this syndrome con-

sists of an increased NRBC count, polycythemia, thrombocytopenia, and a decreased leukocyte count. The different "signs" of this syndrome may be explained by one common pathogenetic mechanism: impaired oxygenation of the fetus. This initiates competition for common stem cells for erythropoiesis, thrombopoiesis, and granulocytopenia in hematopoietic tissue, shunting these stem cells in the direction of erythropoiesis at the expense of thrombopoiesis and granulocytopenia. Experimental studies clearly support such an interdependency between different lines of hematopoietic cell differentiation.⁶

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1. Philip AGS, Tito AM. Increased nucleated red blood cell counts in small for gestational age infants with very low birth weight. *AJDC*. 1989;143:164-169.

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In Reply.—The comments by Dr Meberg provide an opportunity to amplify our discussion and to acknowledge that we had overlooked his article published in 1978.¹ The possibility of selective stimulation of stem cells in the direction of erythropoiesis appealed to us, which is why we reported that thrombocytopenia and leukopenia were not uncommon and associated with increased NRBC counts in SGA infants. We reported in the "Results" section that "Contrary to expectation, SGA infants with marked increase in NRBC counts did not demonstrate high hematocrit values . . ."

As we mentioned, others have noted thrombocytopenia and neutropenia in SGA infants. Brazy et al² noted a high incidence of thrombocytopenia and neutropenia in infants born to mothers with severe hypertension, many of whom (39%) were SGA. McIntosh

et al³ described these findings in association with increased NRBC counts in extremely low-birth-weight SGA infants. They also postulated that marrow stem cells may be more committed to producing cells of the red blood cell series in utero, but noted that no bone marrow studies have been reported in these SGA infants.

One piece of evidence that does not fit neatly with the selective stem-cell stimulation theory deals with hematopoietic progenitors in cord blood. Issaragrisil⁴ showed that although erythroid progenitors correlated well with the number of erythroblasts, so too did granulocyte-monocyte progenitors. However, Christensen et al⁵ have demonstrated in preterm infants that granulocyte-macrophage progenitors may be unable to increase neutrophil production "in times of need," such as bacterial infection, leading to neutropenia. To my knowledge, this has not been evaluated in SGA infants.

Perhaps we did not see elevated hematocrit values because our sights were set too high (>0.60). There is recent evidence that fetal hematocrit values have a mean value of 0.41 between 26 and 30 weeks' gestation,⁶ so values between 0.50 and 0.60 may be elevated. Such levels would not normally be classified as "polycythemia" (erythrocythemia).

Despite these minor reservations, I am inclined to agree with the pathogenetic mechanism proposed by Dr Meberg and also that there probably is a "hematologic syndrome of the SGA infant."

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Cat-scratch Disease Therapy

Sir—Since my original experience¹ with cat-scratch disease, I have remained interested in it and impressed with its stubborn resistance to therapy.

During the last 3 months I have treated 11 children (Table) for cat-scratch disease with 20 mg/kg of trimethoprim-sulfamethoxazole twice daily for 7 days, and all 11 have shown prompt improvement. The enlarged nodes were visible, very tender, and firm without palpable suppuration. All of these patients were treated with trimethoprim-sulfamethoxazole twice daily within 7 days of the onset of their enlarged gland. The lymph nodes became nontender in 4 to 6 days, and smaller by 7 to 10 days. They were 10 mm or smaller by 3 weeks in all cases. Nine of 11 patients had a history of exposure to cats. There was a primary inoculation lesion (usually a scratch) in 7 of these 11 patients. My prior experience had been to treat them with penicillins or cephalosporins, and the disease would run the usual 4- to 6-week course. After 1 week the nodes were always the same size or larger. Several patients had previously required needle aspiration of pus after 4 to 6 weeks of continued painful lymph node swelling. None of the 11 recent patients required this.

These patients did not have pharyngitis, significant fever, otitis, or evidence of cellulitis to suggest other causes of lymphadenitis. Blood tests for bacterial and viral titers were not done. It is probably significant that a recently described patient with neutropenia and oculoglandular syndrome finally showed improvement when trimethoprim-sulfamethoxazole was given.² My experience with the disease is in agreement with the reported seasonal incidence,³ finding it to be more common in the fall and more common in Georgia than Long Island, NY. It is the most common cause of painful regional lymphadenitis seen in Georgia. It is thought to be caused by a gram-negative bacteria acquired from cats.^{4,5}

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Circumcision and Urinary Tract Abnormalities

Sir—In a study recently published in *AJDC*, Herzog¹ showed that noncircumcision is a significant risk factor for urinary tract infection (UTI) in infants up to 12 months of age, an assertion that supports earlier studies by Wiswell et al.^{2,3} In Herzog's study 8 (26%) of 31 uncircumcised male infants with UTI were found to have anatomic abnormalities detected roentgenographically. It is further pointed out that in three of four previous studies of the incidence of urinary tract abnormalities in infants less than 1 year of age with UTI, the frequency of roentgenographic abnormalities is even greater. Though circumcision status was not mentioned in those studies, "they were from countries where neonatal circumcision is not routine."¹ The implication is that noncircumcision puts an infant at risk for an anatomic abnormality of the urinary tract. This implication is by no means proved and, in fact, can and has been misconstrued, especially in the popular press, as further justification to support newborn circumcision. The eight urinary tract abnormalities detected in Herzog's study—posterior urethral valves, ureteropelvic junction obstruction, two cases of grade IV reflux, and four cases of

Summary of 11 Patients With Cat-scratch Disease

Age, y	Tender Lymph Node Site	Original Size of Node, cm	Exposure to Cats*	Skin Test Positive*	Therapy	Improvement Within First Week*	Size of Node 1 wk After Therapy, cm
14	Axilla	4	+	+	Trimethoprim-sulfamethoxazole	+	3
6	Axilla	3	+	+	Trimethoprim-sulfamethoxazole	+	2
2	Axilla	4	+	Not done	Trimethoprim-sulfamethoxazole	+	2
13	Postauricular	2	—	+	Trimethoprim-sulfamethoxazole	+	2
3	Inguinal	3	+	Not done	Trimethoprim-sulfamethoxazole	+	1
8	Inguinal	3	—	+	Trimethoprim-sulfamethoxazole	+	2
12	Preauricular	2	+	+	Trimethoprim-sulfamethoxazole	+	1
9	Axilla	4	+	+	Trimethoprim-sulfamethoxazole	+	3
12	Cervical	4	+	+	Trimethoprim-sulfamethoxazole	+	2
7	Axilla	4	+	+	Trimethoprim-sulfamethoxazole	+	3
9	Cervical	5	+	+	Trimethoprim-sulfamethoxazole	+	3

*Plus sign indicates positive or present; minus sign, negative or absent.

grade II reflux—were almost certainly present from birth and are likely to have been factors that contributed to the development of UTI rather than the result. In these infants noncircumcision may have been advantageous because it contributed to the development of UTI early in life, prompting roentgenographic investigations that detected an occult urologic abnormality. Noncircumcision status as a known risk factor for UTI may lead to earlier and more appropriate urine sampling from a male infant with fever or any other nonspecific sign of illness. While studies like those of Herzog and Wiswell et al are valuable, they do not justify routine circumcision of the newborn.

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Sir—In the March 1989 issue of *AJDC*, Herzog¹ presented reports of 36 infants with positive urine culture during routine workup for acute illness. All these infants were uncircumcised, whereas this was true only for 32% of the control population. Of the 31 infants who underwent roentgenographic studies, 4 had grade II and 2 grade IV reflux, 1 had posterior urethral valve with hydronephrosis, and 1 had ureteropelvic junction obstruction and hydronephrosis. The authors concluded that noncircumcision is a highly significant risk factor for UTI in infants.

There is a recent surge of interest and controversy about the association of infantile UTI and periurethral bacterial flora with noncircumcision.²⁻¹⁴ On one side of the spectrum circumcision is considered to be a prophylactic measure against UTI in infants (Wiswell and his collaborators^{3,8,10,13,14}), while on the other, the need to perform surgery on 96 to 98 infants to prevent

two to four UTIs is questioned.⁵⁻⁷ It is also suggested that adequate hygiene could be a less invasive way of preventing UTI than circumcision.⁷ Some opponents of routine circumcision are concerned about the small but existing surgical risk; others focus on the pain associated with the procedure. In addition, the significance of UTI for future complications is not well known.

Based on recent evidence,^{2-4,8} a new Ad Hoc Task Force on Circumcision appointed by the American Academy of Pediatrics is expected to change the previous recommendation¹⁵ so that the potential benefit of circumcision in avoiding infantile UTI is included in the parental information.

From the present study, however, a new conclusion needs to be considered. It appears that noncircumcision has a definite advantage in aiding the early detection of potentially serious anatomical deformities of the genitourinary system by allowing the development of UTI relatively early in the course. In such cases surgical intervention or close medical follow-up may be initiated to ensure better long-term outcome. While 2% to 4% of circumcised boys have the clear advantage of avoiding UTI, a fact of yet uncertain significance, approximately 25% of those 2% to 4% "lucky ones" may turn out to be handicapped because their anatomic defects will be discovered only later in life in a more advanced state.

Therefore, with routine circumcision we may improve the statistics of UTI in male infants younger than 1 year, but the final outcome may be unfavorable after this arbitrary end point. This fact should also be disclosed to parents when they decide about circumcising their sons.

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In Reply—Dr Hopp and Drs Rockney and Caldamone discuss an important aspect of the relationship between UTI, noncircumcision, and anatomic abnormalities of the urinary tract. I did not mean to imply that the presence of a foreskin causes anatomic abnormalities—that seems highly improbable. Rather, I agree that noncircumcision is an additional risk factor that, by provoking UTI, can aid in detecting anatomic abnormalities that are already present. This may be of long-term benefit to the child, as Dr Hopp suggests. However, it is difficult to advocate catching one disease (UTI) to prevent another, albeit a more serious one (possible end-stage renal disease from reflux). Fortunately a safer screening test is being widely used—prenatal ultrasound. More and more congenital urologic abnormalities are being detected by prenatal ultrasound, which may someday render this whole discussion moot.

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Breath Hydrogen in Preterm Infants

Sir—I read the report by Cheu et al that supports the claim that breath hydrogen excretion might be useful in the management of the premature neonate at risk for developing necrotizing enterocolitis (NEC). The authors suggest that

it is conceivable that many premature infants undergo a period during which their gut represents an environment conducive

to rapid bacterial growth. During this critical period NEC will develop if bacteria of sufficient virulence proliferate in a quantity sufficient to overcome the bowel's defenses. The degree to which the balance between bacterial growth and bacterial defenses is upset would then determine the severity of the disease, ranging from no disease or feeding intolerance to mild or fulminant NEC.

They do not, however, acknowledge important observations, helping to further substantiate their interpretation.

Stevenson et al² showed that the changes in the number of hydrogen-producing bacteria in the gut contributes to changes in the pulmonary elimination of hydrogen in preterm infants who do not have clinical evidence of carbohydrate intolerance. The change in (Δ) end-tidal hydrogen correlated with the Δ total colony count of Enterobacteriaceae in healthy preterm infants who were in an apparent steady state of nutrition. The intestinal colonization of the preterm infants we studied was characterized by a paucity of anaerobes and biotypes of Enterobacteriaceae. The conspicuous absence of anaerobic bacteria and their eventual appearance in a few infants is very different from the normal pattern of colonization described by Long and Swenson,³ possibly because 83% of the infants we studied had recently received antibiotics. Finally, we concluded that breath hydrogen measurements might provide "a means of detecting changes in gastrointestinal flora and possibly overgrowth with single biotypes of Enterobacteriaceae in preterm infants. This information will permit an evaluation of whether potentially pathogenic Enterobacteriaceae contribute to certain disease states, such as necrotizing enterocolitis and sepsis."²

In a review of the methods and clinical applications of breath hydrogen analysis,⁴ we pointed out that the interpretation of breath hydrogen analysis results in neonates and young infants remains difficult for the reasons below:

1. Although in the adult, a fairly constant fraction of total hydrogen production is excreted in breath, providing a reliable indicator of total colonic production of hydrogen, the fraction of hydrogen excreted in the breath of neonates and young infants cannot be assumed to be the same. We recently reported on simultaneously measured excretion rates of end-tidal hydrogen concentration plus breath

and total body hydrogen (breath hydrogen plus flatus hydrogen).⁵ The fractional breath hydrogen excretion in these infants was 48% (33% to 69%), compared with 21% reported in adults. The correlation coefficient for end-tidal-derived hydrogen excretion and directly measured breath hydrogen excretion rates was .95. We concluded that the proportion of total hydrogen excreted in the breath of neonates is higher compared with adults, suggesting that caution must be exercised when interpreting newborn breath hydrogen measurements using adult norms.

2. Because hydrogen is a byproduct of fermentation by colonic bacteria acting on unabsorbed carbohydrate, its total production is influenced by factors that affect the ability of the flora to act on this carbohydrate. Such factors include (a) the type of bacteria; (b) the number of bacteria; (c) the amount of carbohydrate reaching the colon; (d) the transit time; (e) the colonic pH that is related to the absorption of volatile fatty acids produced in association with fermentation; and (f) the presence of small-bowel bacterial overgrowth.

3. Procedures to ensure the reliability of breath sampling in neonates need to be used. Cheu et al argue that the use of carbon dioxide excretion to standardize hydrogen excretion is a logical strategy for improving the accuracy of hydrogen excretion values. We are in agreement with this conclusion. We also concur that, as minute ventilation increases, the hydrogen concentration can decrease more rapidly than does the carbon dioxide concentration in expired gas. Because one of the major possible confounding factors for a false-negative screening test would be environmental contamination of the sample, we suggest that the use of end-tidal carbon monoxide as an internal standard for reducing the error in end-tidal hydrogen measurements due to contamination of repeated breath samples with nonalveolar gas might also be a useful procedure.⁶ In fact, for individual infants, this correction procedure may reveal more marked short-term fluctuations in true alveolar hydrogen concentration.

In summary, we are grateful to see that breath hydrogen excretion might be useful in the management of the premature neonate at risk for the development of NEC. Its successful application as a screening test, however,

will depend on procedures for sample standardization and for ensuring repeated sampling of individual infants over time. Furthermore, a large multicenter collaborative study is needed to define the true positive and negative predictive accuracies of the breath hydrogen screening test for NEC.

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Low-Dose Alternate-Day Corticotropin Therapy in the Treatment of Childhood Seizures

Sir.—Corticotropin was used to treat 17 children with intractable epilepsy other than infantile spasms. Treatment was brief, averaging 5.9 weeks, with 3 to 6 IU/kg per day as the starting dose. Remission of seizures, persisting for a year or more, was achieved in 5 (55.6%) of 8 children with myoclonic/akinetic seizures but in none of the 9 patients with intractable generalized clonic or complex partial seizures (GTC-CPS) ($P < .01$, Fisher's Exact Test). No patient suffered serious side effects.

A short course of low-dose corticotropin therapy appears useful for some children with myoclonic/akinetic seizures but not for patients with intractable GTC-CPS epilepsy.

Corticotropin has been recognized as a valuable anticonvulsant since 1950.¹ Its use, however, has been mainly confined to children with infantile spasms. In 1983, Snead et al² reported that corticotropin completely controlled the

seizures in all 52 patients studied with infantile spasms and in 74% of 64 children with other types of intractable seizures. Their protocol began with 150 U/m² of body surface area daily for 1 week. The dose was then tapered over the subsequent 11 weeks. Significant side effects with high-dose corticotropin therapy have been reported by other authors and include irritability, hypertension, vomiting, gastrointestinal tract bleeding, and peripheral edema.^{2,3}

As corticotropin is very effective in the treatment of infantile spasms, we hypothesized that myoclonic seizures in older children might be more responsive to such therapy than other types of seizures. We studied the effect of a low-dose protocol of corticotropin therapy in 17 children with myoclonic/akinetic seizures or intractable GTC-CPS epilepsy.

Patients and Methods.—In 1983 we standardized our protocol for the use of corticotropin in the treatment of children with seizures. Our typical regimen was a 6-week course, usually starting with 4 to 6 IU/kg per day of corticotropin gel given as a daily intramuscular injection for 1 week. A lower starting dose was used in older children, but the average initial dose was 4.1 IU/kg per day. In the second week corticotropin was given every other day at the same dose as during week 1 and was subsequently tapered to an every-other-day regimen to complete a 6-week course. All patients started to receive treatment as inpatients in the neurology ward of our hospital. Parents were taught to give the injections, and treatment was continued at home. Two children were discharged to the care of their parents within 24 hours of commencing corticotropin therapy.

Follow-up consisted of weekly physical examinations and blood pressure measurements during treatment, usually by the patient's family physician. All children were assessed in our seizure clinic prior to starting therapy and at its completion. All patients have been followed up for at least 3 years after corticotropin therapy and were seen in person in 1988.

We reviewed the records of all children who were treated with a 6-week or shorter course of corticotropin for seizures in our institution between 1983 and 1985. The I. W. K. Hospital for Children, Halifax, Canada, serves as the referral center for all children with epilepsy in the Canadian Maritime Provinces (population, approximately 1.5 million).

The charts were reviewed for seizure type, neurological and developmental status at the onset of treatment, other clinical abnormalities, and age at the onset of seizures and treatment. The electroencephalograms (EEGs) were all interpreted by one of us (P.R.C.). The dose, duration, and efficacy of corticotropin and any side effects were

recorded.

Seizure categories were defined according to the clinical seizure type, with those who had predominantly myoclonic seizures, other than infantile spasms, or akinetic seizures being classified as myoclonic/akinetic. Those with intractable GTC-CPS epilepsy had either generalized clonic or complex partial seizures that had not been controlled by at least four anticonvulsant drugs (mean, 6.5 drugs; range, four to eight drugs). Infantile spasms were not considered.

Among those with intractable GTC-CPS epilepsy, seven had predominantly generalized tonic-clonic seizures while two had mainly complex partial seizures. Two of the children with tonic-clonic seizures also had akinetic seizures and two others also had atypical absence epilepsy. Another child in the GTC-CPS group had gelastic seizures that subsequently resolved spontaneously.

The average age of those with myoclonic seizures (eight patients) was 5.7 years (range, 1.5 to 10.5 years) and of the intractable epilepsy group (nine patients) was 6.4 years (range, 2.5 to 14 years). The average interval between seizure onset and corticotropin treatment was 4.66 years (range, 2 to 13.5 years) for those with intractable GTC-CPS seizures and 2.75 years (range, 1 week to 7.5 years) for those with myoclonic seizures.

The duration of corticotropin treatment for all children with myoclonic/akinetic seizures was 6 weeks. Eight children with intractable GTC-CPS epilepsy were treated for 6 weeks, but one was treated for 4 weeks (average, 5.8 weeks).

The number of seizures was assessed by the parents. As they may not have recognized all episodes, we limited the estimation of response to two categories: *positive* when there was complete seizure control for 6 months or longer and *negative* when there was less than 100% decrease in the seizure frequency or when the response persisted for less than 6 months.

Results were analyzed in the form of a 2 × 2 table, using Fisher's Exact Test.

Results.—In the myoclonic/akinetic group five children (62.5%) had positive responses and three (37.5%) had negative ones. None of the nine with intractable GTC-CPS epilepsy had a positive result ($P < .01$, Fisher's Exact Test).

Among the children who had positive responses, all had a period with no witnessed seizures that lasted from 10 months to 3 years. Two patients continue to be seizure free after 3 years.

Neurological or developmental abnormalities prior to the onset of treatment did not influence the response to therapy. In those with myoclonic seizures one of five was developmentally normal in the group that responded, but all those who had a negative response were developmentally delayed. In the intractable GTC-CPS epilepsy group there were two children who were developmentally normal, although neither responded to corticotropin therapy.

The interval between the commencement of corticotropin therapy and the onset of seizures was similar in both the children who responded and those who did not in the myoclonic epilepsy groups, at 2.75 and 2.83 years, respectively.

The side effects in our patients consisted of stimulus-induced irritability, acne, and a mild cushingoid appearance. Hypertension did not occur, and other serious adverse effects were not observed.

A remarkable improvement in the EEG was seen in two of the five children with positive responses, as detailed below.

Patient Reports.—Patient 1 was delivered at 27 weeks' gestation and suffered an intraventricular hemorrhage with subsequent hydrocephalus, seizures, profound mental retardation, and spastic quadriplegia. He was treated with phenobarbital, but at 17 months of age myoclonic seizures were noted. He was treated with corticotropin for 6 weeks with an initial dose of 5.7 IU/kg per day. The seizures stopped prior to the completion of the course of corticotropin therapy. His EEG was dominated by high-voltage delta background activity with frequent polyspike and wave epileptiform discharges at 2 Hz prior to the start of corticotropin therapy and showed remarkable improvement when repeated 2 weeks following the completion of the course. At 22 months of age he was weaned from phenobarbital therapy. He remained seizure free until 27 months of age when he had a further generalized clonic seizure, which was followed by treatment with diphenylhydantoin. He has remained seizure free at 56 months of age.

Patient 2 was normal until 4 years of age when frequent myoclonic/akinetic seizures began. His EEG showed multifocal spikes but findings of all other investigations were normal. He had two generalized clonic seizures prior to starting corticotropin therapy. The initial dose of corticotropin was 5 IU/kg per day, and the course, which lasted 6 weeks, resulted in a complete resolution of his seizures. Now, at age 6½ years, he is neurologically normal and is free of seizures while receiving no medication.

Patient 3, a 14½-year-old girl, was treated for a medulloblastoma that occurred at 2½ years of age. Her residual deficits include mental retardation, leukoencephalopathy and frequent clonic and complex partial seizures. Multiple anticonvulsant drug failed to control her epilepsy, but at age 1 years she had almost exclusively myoclonic seizures. Despite a trial of valproic acid, she continued to have about 10 seizures per day and, at age 10½ years, she was given a 6 week course of corticotropin therapy (starting dose, 3.75 IU/kg per day). Her seizure stopped within 1 week of commencing corticotropin therapy, and she remained seizure free for 12 months. The EEG before corticotropin therapy was dominated by synchronous spike and slow-wave discharges, but when repeated 1 month later no epileptiform discharges were seen. Her myoclonic seizures returned; a second course of corticotropin therapy was without benefit.

Patient 4 was a developmentally delayed girl with XXX syndrome and epilepsy. Her seizures were predominantly myoclonic, and she was treated with multiple anticonvulsant drugs without success. At 6 years of age she received a 6-week course of corticotropin therapy, which resulted in 1 year without seizures. When her seizures recurred, a second course of corticotropin therapy was given but failed to control her seizures.

Patient 5 was born at 37 weeks' gestation but suffered an intraventricular hemorrhage in the neonatal period with a residual porencephalic cyst and hydrocephalus. When seen at 26 months of age he had a 6-month history of frequent myoclonic seizures (15 to 25 per day). Control was not achieved with valproic acid, and at 30 months of age he was given a 6-week course of corticotropin therapy (starting dose, 3 IU/kg per day). After 2 weeks of therapy his seizures stopped, and 2 months later valproic acid therapy was discontinued. He presented 14 months later with headaches due to a large intracranial tumour that had not been present on previous cranial computed tomographic scans. Following therapy for his tumor, further seizures occurred and he died at 6 years of age.

Comment.—In 1950, Klein and Livingston¹ reported a brief improvement in seizure control in four of six patients treated with corticotropin. The mode of action of corticotropin as an anticonvulsant remains obscure, although there is general agreement that it is beneficial in the treatment of infantile spasms. It is known, however, that dense axonal networks that contain corticotropin are widely distributed in the brain.⁴ It has been speculated that corticotropin may act as a neurotransmitter or neuromodulator that can regulate the number of γ -aminobutyric acid (GABA) receptors in specific brain regions.⁶ In the developing rat brain, corticotropin reduces seizure susceptibility and has no long-term adverse effects on neuronal growth.⁶

The evaluation of corticotropin in the treatment of epilepsy has been complicated by the variability of both the

dosage and duration of treatment in the published studies.⁷ In 1983, Snead et al⁸ found that 74% of 64 children with intractable epilepsy other than infantile spasms had complete seizure control following treatment with corticotropin. Long-term control of seizures was obtained in only 56% (nine patients) with myoclonic seizures other than infantile spasms and in 33.3% (six patients) with other types of intractable seizures.

We separated our patients with myoclonic seizures from those with other types of seizures as we postulated that infantile spasms and therefore possibly other myoclonic seizures are most responsive to corticotropin.

We found that five patients (62.5%) with predominantly myoclonic seizures had prolonged improvement in their seizure control, all becoming essentially seizure free for at least 1 year. The remaining three children (37.5%) had no change in their seizure frequency. No patient with intractable GTC-CPS epilepsy benefited from corticotropin therapy. This difference in response was statistically significant ($P < .01$).

Our results are more consistent with the data reported by Snead et al⁸ in a subsequent study. In this second study, they found that eight of nine patients with severe mixed seizure disorders initially did well but that all except one had a recurrence of seizures as the corticotropin dosage was tapered.

The absence of serious side effects in our patients may have been the result of our regimen of alternate day medication after the first week of treatment. This protocol is also more acceptable to parents and is less expensive than most other corticotropin regimens.

We conclude that corticotropin at an initial dose of 2 to 6 IU/kg per day for 1 week and then alternate-day treatment in decreasing doses for a total 6-week course is a useful and safe treatment for older children with myoclonic epilepsy. We were unable to demonstrate

the value of corticotropin in treating other types of intractable GTC-CPS epilepsy.

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In Other AMA Journals

ARCHIVES OF OPHTHALMOLOGY

Retinal Hemorrhage Predicts Neurologic Injury in the Shaken Baby Syndrome

W. Scott Wilkinson, MD; Dennis P. Han, MD; Marshal D. Rappley, MD; Clyde L. Owings, MD (*Arch Ophthalmol*. 1989;107:1469-1471)

NEW FROM McNEIL

**Pedia
Profen™**

Ibuprofen Suspension 100 mg/5 ml

A new therapeutic alternative for fever

Antipyretic efficacy

In children with temperatures greater than 102.5°F, ibuprofen 10 mg/kg is more effective than ibuprofen 5 mg/kg or acetaminophen 10 mg/kg.¹

PediaProfen is indicated for the reduction of fever in children 6 months and older.

Longer duration of action than acetaminophen for fever^{1,2}

Ibuprofen 10 mg/kg provides up to 8-hour relief. That means fewer interruptions in the family's work, school, or sleep schedules.

Safety profile*

See brief summary of Prescribing Information. Significant adverse effects are reported with NSAIDs. Serious as well as minor side effects can occur with long-term use of high-dose ibuprofen. In clinical studies with over 400 pediatric patients, no significant adverse reactions were reported during short-term therapy for fever.²

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Designed for compliance; well liked by patients in clinical studies.²

References:

¹Walson PD, et al. Ibuprofen, acetaminophen and placebo treatment of febrile children. *Clin Pharmacol Ther.* 1989;46:9-17. ²Data on file, McNeil Consumer Products Company.

From the children's fever relief specialist

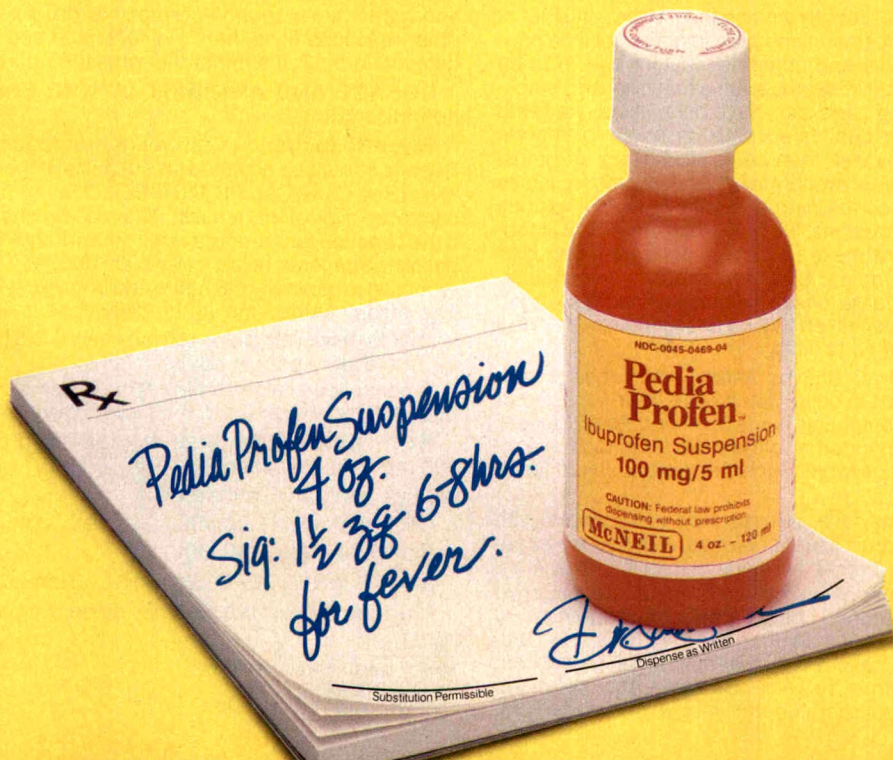
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*Please see Brief Summary of Prescribing Information on the last page of this advertisement.

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Ibuprofen Suspension
100 mg/5 ml



New **PediaProfen**TM

Ibuprofen Suspension 100 mg/5 ml

The following is a brief summary only. Before prescribing, see complete prescribing information in **PediaProfen** labeling.

INDICATIONS AND USAGE: **PediaProfen** is indicated for the reduction of fever in patients aged 6 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CLINICAL PHARMACOLOGY: Controlled clinical trials comparing doses of 5 and 10 mg/kg ibuprofen and 10-15 mg/kg of acetaminophen have been conducted in children 6 months to 12 years of age with fever primarily due to viral illnesses. In these studies there were no differences between treatments in fever reduction for the first hour and maximum fever reduction occurred between 2 and 4 hours. Response after 1 hour was dependent on both the level of temperature elevation as well as the treatment. In children with baseline temperatures at or below 102.5°F both ibuprofen doses and acetaminophen were equally effective in their maximum effect. In those children with temperatures above 102.5°F, the ibuprofen 10 mg/kg dose was more effective. By 6 hours children treated with ibuprofen 5 mg/kg tended to have recurrence of fever, whereas children treated with ibuprofen 10 mg/kg still had significant fever reduction at 8 hours. In control groups treated with 10 mg/kg acetaminophen, fever reduction resembled that seen in children treated with 5 mg/kg of ibuprofen, with the exception that temperature elevation tended to return 1-2 hours earlier.

CONTRAINDICATIONS: **PediaProfen** should not be used in patients who have previously exhibited hypersensitivity to ibuprofen, or in individuals with all or part of the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy. Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving **PediaProfen**, the drug should be discontinued and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with ibuprofen, therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

PediaProfen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation, but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range), in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying

hemostatic defects, **PediaProfen** should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients on **PediaProfen** should report to their physician signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

In order to avoid exacerbation of disease of adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of **PediaProfen** may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Safety and efficacy of **PediaProfen** in children below the age of 6 months has not been established.

Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurs in rats. Administration of **PediaProfen** is not recommended during pregnancy.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Adverse reactions occurring in 3% to 9% of patients treated with ibuprofen: nausea, epigastric pain, heartburn, dizziness, rash. *Adverse reactions occurring in 1% to 3% of patients:* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract, headache, nervousness, pruritus, tinnitus, decreased appetite, edema, fluid retention (generally responds promptly to drug discontinuation). Still other reactions (less than 1 in 100) have been reported, and are detailed in the full summary of prescribing information.

DOSAGE AND ADMINISTRATION: Shake well prior to administration.

Fever Reduction in Children 6 months to 12 years of age Dosage should be adjusted on the basis of the initial temperature level (See CLINICAL PHARMACOLOGY for a description of the controlled clinical trial results). The recommended dose is 5 mg/kg if the baseline temperature is less than 102.5°F or 10 mg/kg if the baseline temperature is greater than 102.5°F. The duration of fever reduction is generally 6-8 hours and is longer with the higher dose. The recommended maximum daily dose is 40 mg/kg.

Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for the relief of pain in adults.

In controlled analgesic clinical trials, doses of ibuprofen greater than 400 mg were no more effective than 400 mg dose.

HOW SUPPLIED: **PediaProfen** Ibuprofen Suspension 100 mg/5 ml (teaspoon)—

orange, berry-vanilla flavored

Bottles of 4 oz (120 ml)..... NDC 0045-0469-1

Bottles of 16 oz (480 ml)..... NDC 0045-0469-2

SHAKE WELL BEFORE USING. Store at room temperature.

Caution: Federal law prohibits dispensing without prescription.

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Growth Retardation

Impaired Height Velocity

Growth results from an increase in cell number and/or cell size. Availability of basic building materials (nutrition) and the ability to utilize them (normal organ systems) influence growth. Genes, the blueprints for the organ systems, determine growth efficiency.^{1,2} Clinical assessment of growth is based on serial measurements of height and weight over time. Change occurring in relation to time is a velocity. In evaluating growth velocity, it should be noted that there may be no measurable growth during a single 3-month period in a normal child.³

See also pp 1282, 1284, and 1287.

Subsequent to birth, height and weight velocity decelerate.^{4,5} Height velocity decelerates from 25 cm/y to a minimal basal velocity of 5 cm/y by the third year of life. Programmed genetic variation as to what basal velocity is achieved, and how rapidly the deceleration occurs for a normal population, is graphically indicated as the percentile rankings on a growth chart.

Individuals who are slow in somatic growth are less growth efficient than the general population and achieve the minimal basal height velocity more rapidly than the general population.⁶ Their heights, when plotted on a growth chart, will be below the third percentile. But, because they are growing at the minimal basal height velocity, a graphic depiction of their height will parallel that of the general population.⁶

Basal height velocity is facilitated by thyroid and growth hormone. Following the onset of puberty, height velocity is accelerated by the sex steroids, androgens and estrogens. Because of their effect on epiphyseal fusion (bone age), the sex steroids

ultimately stop height velocity, and adult height is achieved.

Height below the third percentile is defined as "short stature." Adults with heights that are less than the third percentile, who were slow in somatic growth during childhood, and whose family members have similar adult heights are referred to as having "familial short stature." During childhood they have bone ages and chronological ages that are comparable. They also have the initiation of puberty by the mean chronological age expected for its onset.

Individuals who were slow in somatic growth during childhood, and whose adult height is greater than the third percentile (usually the fifth percentile or more), are referred to as having "constitutional short stature." During childhood their bone age is less than their chronological age. They also have the initiation of puberty at a later age than the mean chronological age expected for its onset.

Short stature is a disadvantage in our society.⁷ In the context of height, bigger is better. A person whose accomplishments are remarkable is spoken of as a "person of stature." The appearance of the short child invites "babying." This contrasts with the favored position of the tall child whose innate abilities are presumed to develop more rapidly than those of the short child. Understandably, since the world of the adult is no less biased, a parent would be most anxious to treat a short child. This would be particularly true for a parent similarly stigmatized.

Because of the commercial availability of biosynthetic growth hormone (GH), medical indications and cost are the only limiting factors for prescribing GH. Physicians are presented with two fundamental questions. First, how

can we recognize (through testing and/or trials of GH therapy) the short child who will benefit from GH treatment? Second, ethically, should a child's limited genetic potential for height be augmented by treatment with GH?

Overlapping results make testing for GH secretion alone unable to identify the individual who is GH deficient. This is true whether the evaluation of GH secretion is direct (overnight secretion,^{8,9} 24-hour integrated secretion,¹⁰ or provocative stimuli testing¹¹⁻¹³) or indirect (somatomedin/insulinlike growth factor 1¹⁴). Only when the testing procedure or procedures are combined with a height velocity that is less than the minimal basal height velocity of 5 cm/y can we identify the individual who is GH deficient. It is, therefore, not possible to determine whether the individual who is growing at a basal height velocity of 5 cm/y is growing at an optimum rate for that individual.

A growth response to treatment with GH has been demonstrated in two categories of subjects: those with impaired height velocity and abnormal results of GH testing (classic growth hormone deficiency¹⁵ and GH neurosecretory dysfunction¹⁶), and those with impaired height velocity and normal results of GH testing (bioinactive growth hormone,^{17,18} "normal variant" short stature,^{14,19-23} Turner's syndrome,²⁴⁻²⁶ Down syndrome,²⁷ intrauterine growth retardation,^{28,29} and, as reported in this issue of *AJDC*,³⁰ subjects with microcephaly). All of the patients in the first category responded to GH treatment. Only some of the patients in the second category responded to GH treatment. By and large, the responders in the second category had delayed bone age, height velocity less than 4 to 5 cm/y, and height less than the first percentile.

Whether it is appropriate to augment limited genetic potential for height with GH treatment should be examined in relation to the possibility of adverse consequences (risks) of this action. No medical treatment is entirely risk free. Recently, adverse or potentially adverse consequences have been recognized in GH-deficient patients treated with GH. Creutzfeldt-Jakob disease, resulting from treatment with GH derived from pituitary glands, was recognized in 1985 and eliminated by utilizing only biosynthetic GH.^{31,32} Suppression of immune function was reported in 1986.³³ The depression of immune function was not associated with ill effects. An increase in the risk of leukemia was reported in 1988.³⁴ From current estimates, the increased risk to an individual GH-treated patient is probably twice the natural risk. Assuming a 10-year GH treatment, this would mean 1 chance in 2400 (0.042%).

The foregoing reports serve to reinforce the caution that GH should never be used indiscriminately. Since GH is essential for growth and development, it would be inappropriate to withhold GH treatment from GH-deficient subjects. Indiscriminate use of GH therapy to treat short children who are not GH deficient is strongly discouraged.

To assess the proper place for GH therapy in the treatment of the short child, we need special knowledge of childhood diseases, growth, and endocrinology. A decision to treat the short child is best left to the pediatric endocrinologist.

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Child Passenger Safety

Past, Present, and Future

All clinical research must be interpreted in its historical context. For studies of motor vehicle occupants, that context has been changing particularly quickly.

Past

Once upon a time, not so very long ago, children were always loose when riding in cars. It was not until 1968 that seat belts were required in cars at all.¹ The very first child passenger restraint law for preschool children went into effect in Tennessee in 1978.

See also p 1317.

The 50th state passed its law in 1984. Surveys by the National Highway Traffic Safety Administration indicated that in 1979, 15% of child passengers 0 to 4 years old were restrained compared with 49% in 1984.²

Present

The expectation that children should be protected when they ride in cars, a fairly new one for our society, is already sufficiently strong that car safety seat use among young children now approaches that of immunizations: in 1989, National Highway Traffic Safety Administration surveys showed 82.5% restraint use by 0- to 4-year-olds in shopping center parking lots.² Thus, the good news is that we have come a long way toward safe travel for our children.

The bad news is that we still have a way to go before we can say that US children are riding safely on every ride they take. There are deficiencies in several areas.

Though children under 5 years old are increasingly riding restrained, the rates of *proper* restraint remain frustratingly low. Thus, although parents now recognize the importance of adequate restraint, they are not success-

fully providing it. Furthermore, restraint use, and, more particularly, restraint misuse, is becoming a factor in injury patterns.³

Children who are beyond the age of child passenger restraint laws are apparently also beyond the full reach of the society's expectation of restraint. National Highway Traffic Safety Administration estimates of seat belt use in children ages 5 to 13 years were 15% in 1984 and 39% in 1988. For 13- to 19-year-old passengers it was even worse: 7% in 1984 and 24% in 1988. This is a tragedy, because passengers who travel restrained have a markedly reduced risk of serious head injury, and thus have a reduced risk of resulting death or permanent neurologic handicap. The National Highway Traffic Safety Administration has estimated that "among front-seat passenger vehicle occupants over 4 years old, safety belts saved about 4,500 lives in 1988... [and] prevented about 119,000 moderate to critical injuries."⁴

Now Agran et al⁵ have demonstrated that seat belts do not work as well as we had hoped for older children: they prevent ejection, but serious injuries still occur, especially with lateral crash impacts. Others have shown that as seat belt use has risen, features of belt restraint are becoming factors in child occupant injury patterns.³

Among older adolescents and young adults, the problem remains the "old" one, nonuse of seat belts.

Some vehicles are exempt from some of the structural safety requirements that passenger sedans must meet (eg, concerning roof strength and passive restraints).

Future

Much work remains before the goal of universal safe transport of child and adolescent motor vehicle occupants is realized. Our work is cut out for us,

though in some areas the specific steps we need to take remain unclear.

Universal proper use of child safety seats will require increasing simplicity and uniformity of safety seats and seat belts (they are now often incompatible). Strong and specific federal standards make sense here.

Gaps in child restraint laws need to be closed to assure that *every* child is covered by the expectation of safe transport. In addition to raising the upper age limit to encompass all children, specific exemptions in various states should be eliminated (eg, exemptions for nonresidents or passengers not in their own family's car). Enforcement, with the goal of universal compliance rather than punishment, is essential.

Seat belt systems should optimally restrain people of all sizes who are too big for current child safety seats. In addition to lap belts, shoulder harnesses—preferably with adjustable anchor points for individuals of varying heights—should be required in *all* seating positions. Booster seats can help to properly position the shoulder belt for younger children. Other types of safety seats may be needed for older children.

Gaps need to be closed in the regulations that mandate which vehicles meet which safety standards. Certainly, vans, mini vans, and other light trucks that are often used as family cars must be designed to protect their occupants as well as sedans do.

The study by Agran et al⁵ suggests that new vehicle standards may be needed to enable vehicles to resist crash intrusions into the passenger compartment and to prevent passenger head impact with front seats.

Means must be found to increase the chances that teenagers will survive our car culture. Steps that are likely to help include the following: air

bags and other nondetachable passive restraints (now finally on the horizon); raising a generation of seat-belted children (facilitated by the steps outlined above for school-aged children); steps to decrease the alcohol indulgence of driving age teens (eg, curfews, raised ages for drinking and driving, and alcohol-free party alternatives); and strict and visible enforcement of seat belt laws for new drivers (ages 16 to 22 years are the years of highest crash risk), with specific and stringent penalties for non-use.

Adequate equipment and care protocols are needed to safely transport premature infants and medically fragile children of all ages. These are beginning to be developed.

Financial obstacles to acquiring child safety seats should be removed as part of the current effort to remove all access obstacles to child health care.

The study by Agran et al⁵ shows that seat belts are good but not yet good enough. Similarly, the effort toward safety for children in cars has come a long way but not far enough.

The American Academy of Pediatrics' "Every Ride a Safe Ride" program is available to provide support to pediatricians and others as we work to both maintain our gains and move ahead.

While we work on the steps outlined above, parents should be urged most strongly to use the available restraint systems as best they can: they are the best we have, and they are a big improvement over that time, not so long ago, when children were always dangerously loose in cars.

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Thanks to Tom Christoffel, JD; Susan Hess (coordinator of the "Every Ride a Safe Ride" program of the American Academy of Pediatrics); Robert Tanz, MD; Mark Widome, MD, MPH (chairman of the Committee on Accident and Poison Prevention of the American Academy of Pediatrics); and Michael Winter (National Highway Traffic Safety Administration Office of Occupant Protection) for assistance in gathering information and organizing ideas for this editorial. Thanks also to Phia Van Guyse for secretarial assistance.

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In Other AMA Journals

ARCHIVES OF INTERNAL MEDICINE Professional Satisfaction of Physicians

Harold R. Reames, Jr, PhD, David C. Dunstone, MD (*Arch Intern Med*. 1989;149:1951-1956)

Physicians Attitudes Toward Cost Containment

Harry L. Greene, MD; Robert J. Goldberg, PhD; Helen Beattie, MPH; Arthur R. Russo, MD; R. Curtis Ellison, MD, MS; James E. Dalen, MD, MPH (*Arch Intern Med*. 1989;149:1966-1968)

Leads From the MMWR

Morbidity and Mortality Report
Centers for Disease Control, Atlanta

Measles Outbreak—Chicago, 1989

AS OF AUGUST 23, 1989, 1123 confirmed cases of measles have been reported to the Chicago Department of Health. Information is available for 1019 (91%) of these cases; 799 (78%) have occurred in preschool-aged children (less than 5 years old), including 340 (33%) children less than 16 months of age (i.e., too young for routine immunization). Blacks and Hispanics have accounted for 955 (94%) of the cases. Four measles-associated fatalities have been reported.

Outbreak-control activities have included intensified surveillance and lowering of the recommended age for measles vaccination to 6 months during the outbreak, with revaccination at age 15 months for children vaccinated before the first birthday. Single-antigen measles vaccine is being used for children before the first birthday, and measles-mumps-rubella vaccine (MMR) is administered to older children. Seven new vaccination clinics

have been established and have administered approximately 21,000 doses of vaccine; door-to-door vaccination teams in high-risk communities have administered an additional 2000 doses of vaccine. Hospital emergency department vaccination clinics have been set up in four locations.

Reported by: RM Krieg, PhD, RW Biek, MD, CR Catania, JW Masterson, MPH, Chicago Dept of Health; R March, Immunization Program, RJ Martin, DVM, Div of Infectious Diseases, Illinois Dept of Public Health. Div of Immunization, Center for Prevention Svcs, CDC. (MMWR vol 38 No. 34).

CDC Editorial Note: This outbreak is similar to others among inner-city populations in the United States in that it involves primarily unvaccinated black and Hispanic preschool-aged children.¹⁻³ The Chicago Department of Health has implemented aggressive outbreak strategies directed toward reaching the highest-risk group, i.e.,

unvaccinated preschool-aged children. Such children are also likely to be a reservoir for transmitting virus to other age groups. As part of the extensive outbreak-control efforts, children are being vaccinated in emergency departments. Provision of vaccine to inner-city children who use these facilities for their primary source of health care should help to increase vaccination levels in patients who receive sporadic health care and may reduce the transmission of measles in emergency department settings.

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Prevalence of Drug Use among Applicants for Military Service—United States, June-December 1988

SINCE JUNE 1988, the U.S. Department of Defense has screened all applicants for military service (including the U.S. Coast Guard) for evidence of marijuana and/or cocaine use as mandated by the National Defense Authorization Act of 1988. Applicants confirmed as cocaine-positive are not eligible for military service for 1 year from the date of screening; those confirmed as marijuana-positive are not eligible for military service for 6 months from the date of screening. Persons who tested positive twice for either drug are not eligible for military

service for 2 years from the date of the second test.¹

A pilot study was conducted during March and April 1988 to determine the prevalence of marijuana and/or cocaine use among applicants before the initiation of the program in June. For the pilot study, applicants were not informed about the drug test. However, because personal identifiers were not recorded, results could not be linked to individual applicants. Urine specimens collected as part of the induction physical examination were sent to three of nine military

laboratories and screened by radioimmunoassay (Roche Diagnostic Systems Abuscreen Test Kits[®]) for marijuana and cocaine. Six thousand (42%) urine specimens were selected at random from approximately 14,200 obtained from 12 of 70 Military Entrance Processing Stations. Four hundred thirty-seven (7.3%) and 108 (1.8%) screened positive for marijuana or cocaine, respectively, or their metabo-

¹Use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

lites, and 42 (0.7%) were positive for both marijuana and cocaine (Office of the Army Surgeon General, unpublished data). Although positive specimens were not confirmed, data from military drug-screening laboratories indicate that at least 85% of cocaine and 90% of marijuana users would have been confirmed positive (Office of the Assistant Secretary of Defense for Health Affairs, unpublished data).

From June through December 1988, 322,256 applicants were informed that a urine specimen would be collected for drug screening at the induction physical examination. Positive specimens were confirmed by gas chromatography/mass spectrometry.** The Headquarters for the U.S. Military Entrance Processing Command² provided demographic data.

Of all applicants tested, 3.5% were positive for marijuana and/or cocaine. Men were 2.6 times more likely than women (3.9%, compared with 1.5%,

**In the initial screening, the following levels indicated positivity: greater than or equal to 100 ng/mL for marijuana and greater than or equal to 300 ng/mL for cocaine. Positivity was confirmed at greater than or equal to 15 ng/mL for marijuana and greater than or equal to 150 ng/mL for cocaine.

respectively) to be positive for marijuana and/or cocaine. Blacks were 1.9 times and Hispanics 1.4 times more likely than whites to test positive (5.6% for blacks and 4.0% for Hispanics, compared with 2.9% for whites). The percentage positive for either drug increased with age (1.3% in 17- and 18-year-olds, compared with 5.3% in greater than or equal to 26-year-olds). Geographic variation for cocaine and/or marijuana ranged from 2.5% in the West North Central to 5.3% in the Mid-Atlantic states. The percentage screened positive for marijuana and/or cocaine varied inversely with education level: the highest prevalence was in applicants who had not graduated from high school (7.5%) and the lowest in those educated beyond a 4-year college degree (0.7%).

Reported by: WF Vogl, CDR, USN (MSC), MR Peterson, LT COL, USAF, BSC, Office of the Assistant Secretary of Defense (Health Affairs), Washington, DC. JS Jewell, LTC, USA, Office of the Army Surgeon General, Washington, DC. Div of Environmental Hazards and Health Effects, Center for Environmental Health and Injury Control, CDC (MMWR vol 38, No. 33).

CDC Editorial Note: This report summarizes the findings of the largest

nonrandom drug testing program in the United States and characterizes evidence of drug use by age, race, and sex in a defined population. Applicants for U.S. military service are a geographically diverse sample of young persons. Extrapolation of marijuana and/or cocaine use in this group to the U.S. population may not be reliable because of social and demographic differences of military applicants in the same age groups. Men and racial and ethnic minorities are overrepresented among applicants.

The decrease in percentage of positives among applicants from the pilot study to the systematic screening program indicates that notifying applicants of the drug-testing program may deter continued use, prompt users to withdraw from the application process, or discourage application for military service.

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First 100,000 Cases of Acquired Immunodeficiency Syndrome—United States

IN JUNE 1981, the first cases of the illness now known as acquired immunodeficiency syndrome (AIDS) were reported from Los Angeles in five young homosexual men diagnosed with *Pneumocystis carinii* pneumonia and other opportunistic infections.¹ Since then, state and territorial health departments have reported greater than 100,000 cases of AIDS and greater than 59,000 AIDS-related deaths to CDC. AIDS is now a major cause of morbidity and mortality in children and young adults in the United States, ranking 15th among leading causes of death in 1988² and seventh among estimated years of potential life lost before age 65 in 1987.³ The first 50,000 cases of AIDS were reported to CDC from 1981 to 1987; the second 50,000 were reported between December 1987 and July 1989.

Although homosexual/bisexual men still account for most reported AIDS cases, intravenous-drug users (IVDUs), their sex partners, and their children represent an increasing proportion of all cases. Of AIDS cases reported before 1985, 63% were homosexual/bisexual men with no history of IV-drug use, 18% were female or heterosexual male IVDUs, and 2% were sex partners or children of IVDUs or their sex partners. In contrast, of the AIDS cases reported in the first 6 months of 1989, 56% were homosexual/bisexual men with no history of IV-drug use, 23% were female or heterosexual male IVDUs, and 4% were sex partners or children of IVDUs or their sex partners. The proportion of AIDS cases among women has also increased from 7% of cases reported before 1985 to 11% of

cases reported in the first 6 months of 1989. Blacks and Hispanics continue to be disproportionately represented among all persons with AIDS and particularly among IVDUs with AIDS. Although most AIDS cases are reported from large metropolitan areas, an increasing proportion are being reported from smaller cities and rural areas. Metropolitan statistical areas with populations less than or equal to 500,000 reported 10% of a U.S. cases before 1985, compared with 19% in 1988.

Reported by: AIDS Program, Center for Infectious Diseases, CDC. (MMWR vol. 38, No. 32)

CDC Editorial Note: The 100,000 AIDS cases reported in the United States as of July 1989 represent the minimum number of persons with s

vere human immunodeficiency virus (HIV)-related disease. Because of the combination of underdiagnosis and underreporting of AIDS cases and severe manifestations of HIV infection that do not meet the CDC AIDS surveillance case definition, reported AIDS cases underestimate the number of persons severely affected by HIV since 1981. The completeness of diagnosis and reporting of AIDS cases varies by geographic region and patient population; however, mortality studies suggest that 70%-90% of HIV-related deaths are identified through national surveillance of AIDS.⁴

The number of AIDS cases are one indication of the larger epidemic of HIV infection. An estimated 1-1.5 million persons are infected with HIV in the United States,⁵ with recent seroprevalence studies suggesting that the actual number is closer to the lower end of this range.⁶ A cohort study of homosexual/bisexual men in San Francisco suggests that 54% of infected persons will develop AIDS within 10 years of infection⁷ and that up to 99% will eventually develop AIDS.⁸ There-

fore, the number of persons with AIDS and other severe manifestations of HIV infection will continue to increase.

AIDS is reportable in all 50 states, the District of Columbia, and U.S. territories. AIDS surveillance has been crucial in identifying characteristics of persons at risk for the disease and modes of transmission and remains extremely important in monitoring trends in severe HIV-related disease, projecting future numbers of AIDS cases and HIV-infected persons, and targeting resources for prevention and treatment efforts. Because persons with AIDS require a broad range of medical services, documentation of these cases is also important in determining current and future health-care needs and costs. AIDS surveillance data together with information from the HIV family of surveys⁶ and HIV infection reporting⁹ are important components of public health programs directed toward controlling HIV infection and assist in providing the most accurate picture of the HIV epidemic in the United States.

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In Other AMA Journals

ARCHIVES OF SURGERY

Heart Transplantation During the First 12 Years of Life

Leonard L. Bailey, MD; Michael Wood, MD; Anees Razzouk, MD; Glen Van Arsdel, MD; Steven Gundry, MD (*Arch Surg.* 1989;125:1221-1226)

The Misconception of Trauma Reimbursement

Marc J. Shapiro, MD; Mary Keegan, RN; Jerry Copeland, ACSW (*Arch Surg.* 1989; 125:1237-1240)

Safety first

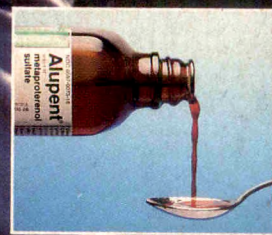


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Please see following page for brief summary of prescribing information.



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Brief Summary of Prescribing Information

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Although rare, immediate hypersensitivity reactions can occur. Therefore, Alupent[®] (metaproterenol sulfate USP) is contraindicated in patients with a history of hypersensitivity to any of its components.

WARNINGS Excessive use of adrenergic aerosols is potentially dangerous. Fatalities have been reported following excessive use of Alupent[®] (metaproterenol sulfate USP) as with other sympathomimetic inhalation preparations, and the exact cause is unknown. Cardiac arrest was noted in several cases.

Alupent, like other beta adrenergic agonists, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or ECG changes. As with other beta adrenergic aerosols, Alupent can produce paradoxical bronchospasm (which can be life threatening). If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

Alupent[®] (metaproterenol sulfate USP) should not be used more often than prescribed. Patients should be advised to contact their physician in the event that they do not respond to their usual dose of a sympathomimetic amine aerosol.

PRECAUTIONS General: Extreme care must be exercised with respect to the administration of additional sympathomimetic agents.

Since metaproterenol is a sympathomimetic amine, it should be used with caution in patients with cardiovascular disorders, including ischemic heart disease, hypertension or cardiac arrhythmias, in patients with hyperthyroidism or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines or who have convulsive disorders. Significant changes in systolic and diastolic blood pressure could be expected to occur in some patients after use of any beta adrenergic bronchodilator.

Information for Patients: Extreme care must be exercised with respect to the administration of additional sympathomimetic agents. A sufficient interval of time should elapse prior to administration of another sympathomimetic agent.

Drug Interactions: Other beta adrenergic aerosol bronchodilators should not be used concomitantly with Alupent because they may have additive effects. Beta adrenergic agonists should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of beta adrenergic agonists on the vascular system may be potentiated.

Carcinogenesis/Mutagenesis/Impairment of Fertility: In an 18-month study in mice, Alupent produced an increase in benign ovarian tumors in females at doses corresponding to 320 and 640 times the maximum recommended dose (based on a 50 kg individual). In a two-year study in rats, a non-significant incidence of benign leiomyomata of the mesovarium was noted at 640 times the maximum recommended dose. The relevance of these findings to man is not known. Mutagenic studies with Alupent have not been conducted. Reproduction studies in rats revealed no evidence of impaired fertility.

Pregnancy Teratogenic Effects: Pregnancy Category C: Alupent[®] (metaproterenol sulfate USP) has been shown to be teratogenic and embryotoxic in rabbits when given orally in doses 620 times the human inhalation dose and 62 times the human oral dose. There are no adequate and well-controlled studies in pregnant women. Alupent should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Oral reproduction studies in mice, rats and rabbits showed no teratogenic or embryocidal effects at 50 mg/kg, corresponding to 310 times the human inhalation dose and 31 times the human oral dose. Teratogenic effects in the rabbit included skeletal abnormalities and hydrocephalus with bone separation.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Alupent[®] (metaproterenol sulfate USP) is administered to a nursing woman.

Pediatric Use Consult package insert for age limit.

ADVERSE REACTIONS Adverse reactions are similar to those noted with other sympathomimetic agents. Adverse reactions such as tachycardia, hypertension, palpitations, nervousness, tremor, nausea and vomiting have been reported.

The most frequent adverse reaction to Alupent[®] (metaproterenol sulfate USP) administered by metered-dose inhaler among 251 patients in 90-day controlled clinical trials was nervousness. This was reported in 6.8% of patients. Less frequent adverse experiences, occurring in 1-4% of patients were headache, dizziness, palpitations, gastrointestinal distress, tremor, throat irritation, nausea, vomiting, cough and asthma exacerbation. Tachycardia occurred in less than 1% of patients.

HOW SUPPLIED Inhalation Aerosol: Each Alupent[®] Inhalation Aerosol contains 150 mg of metaproterenol sulfate as a micronized powder in inert propellants. Each metered dose delivers through the mouthpiece 0.65 mg metaproterenol sulfate (each mL contains 15 mg). Alupent Inhalation Aerosol with Mouthpiece (NDC 0597-0070-17), net contents 14g (10mL), equipped with blue protective cap. Alupent Inhalation Aerosol Refill (NDC 0597-0070-18), net contents 14g (10 mL).

Store between 59°F (15°C) and 77°F (25°C). Avoid excessive humidity.

Inhalation Solution: Alupent Inhalation Solution is supplied as a 5% solution in bottles of 10 mL or 30 mL with accompanying calibrated dropper. Store below 77°F (25°C). Protect from light. Do not use the solution if it is brown or has a precipitate.

Alupent Inhalation Solution Unit-dose Vial is supplied as a 0.4% or 0.6% clear colorless or nearly colorless solution containing 2.5 mL, with 25 vials per box. Store below 77°F (25°C). Protect from light. Do not use the solution if it is brown or has a precipitate.

Syrup: Alupent is available as a cherry-flavored syrup, 10 mg per teaspoonful (5 mL), in 16 fl. oz. bottles. Store below 86°F (30°C). Protect from light.

Tablets: Alupent is supplied in two dosage strengths as scored, round white tablets in bottles of 100. Tablets of 10 mg coded BI/74. Tablets of 20 mg coded BI/72.

Storage for bottles: Store below 86°F (30°C). Protect from light.

Storage for blister samples. Store below 77°F (25°C). Protect from light.

Consult package insert before prescribing.

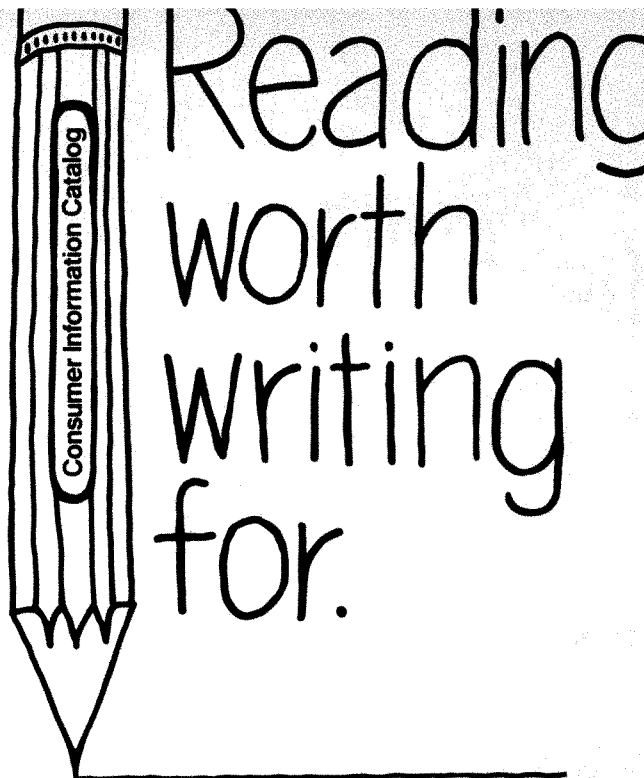
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Book Review

Linear Growth Retardation in Less Developed Countries, edited by J. C. Waterlow, 313 pp, \$40, New York, NY, Raven Press, 1988.

This book is a record of the proceedings of the 14th Nestle's Nutrition Workshop held in Thailand in March of 1986. It is a series of reports and transcripts of the discussions provoked by each presentation. The list of participants is formidable and includes leading experts in linear growth velocity and experts in the circular relationship between poverty, malnutrition, and growth. Presenters included individuals from countries in the developed and developing world.

The workshop recognized the increased frequency of stunting in the less developed parts of the world. The prevalence of stunting can be used as an index of the poverty level in a given region or country. Although this was an important underlying theme of the proceedings, participants emphasized the biologic determinants and the physical handicaps associated with stunting. The discussions following each presentation were as open and interesting as the reports; they indicate the present state of our knowledge and suggest a multitude of projects to be undertaken that would increase our understanding of the process of stunting and the sequelae of short stature.

J. C. Waterlow opened the volume with a chapter titled "Natural History of Stunting." This is followed by chapters on epidemiology, the best time increments to monitor length, and the relationship between poverty and stature. Three chapters discuss the relative influence the intrauterine environment, genetic endowment, and hormones exert on growth. The role that calcium, zinc, and protein play in determining growth velocity is the subject of the next two chapters. David Narborro from Liverpool, England, wrote a very interesting chapter on the role of infection in growth retardation. The risk of morbidity in the stunted child is presented by Andrew Tomkins from London, England, and W. Van Lerberghe from Belgium discussed the effect retarded linear growth has on mortality. Marta Colombo from Chile presented data on the relationship between mental development and stunting. G. B. Spurr from Wisconsin wrote a provocative chapter on body size and work capacity. C. Gapalan from the Nutrition Foundation of India completed the volume on a political note, with a report titled "Stunting: Significance and Implications for Public Health Policy." Hence, we are taken full circle with an abundance of exciting and stimulating information along the way.

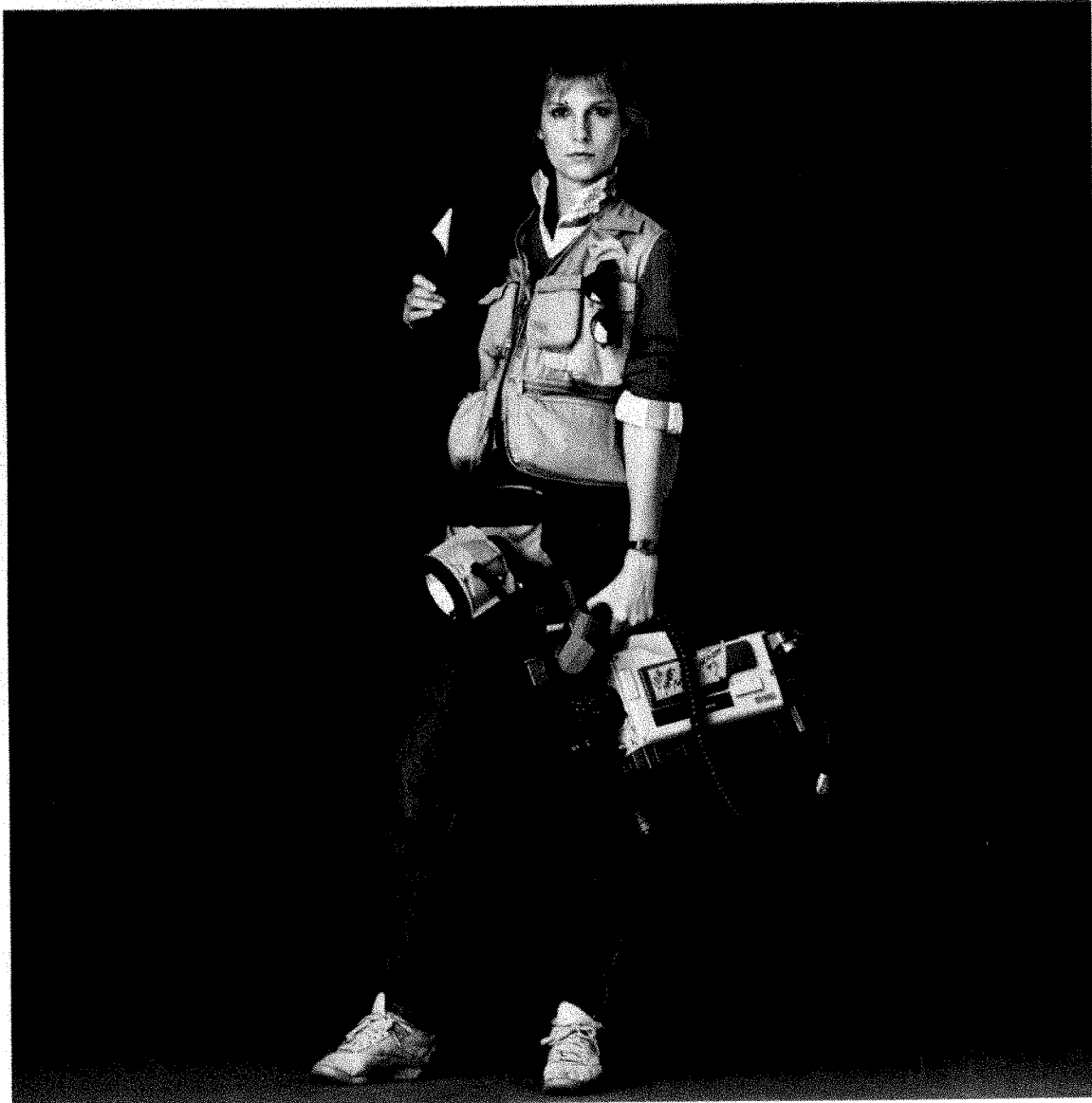
These are a few of the gems gleaned from this workshop: (1) "Think of stunting (as measured by low height for age) as the cumulative result of many events that disrupt growth

rates in length and cause wasting. Wasting (as measured by low weight for height), on the other hand, is a snapshot reflecting recent disruptive events." (2) As the seasons change so may the velocity of linear growth. In developed countries, children grow faster in height in the spring and less rapidly in the fall. In developing countries, other factors, such as culture and the availability of food, have a greater effect on growth velocity. (3) The intrauterine environment is the major determinant of the length of the newborn, as the fetal genome accounts for only 20% of the variance in birth size. During the first 12 to 24 months of life, genetic influences seem to predominate, provided there are no adverse environmental circumstances, such as lack of food, severe infections, or deprivations. (4) Strenuous maternal activity decreases placental perfusion with a postulated adverse effect on fetal nutrition. (5) If length velocity is slowed in the first 3 years of life (as is so frequently the case in the developing world), the result is a stunted adult (even if growth velocity returns to normal after the third year of life). "If stunting can be prevented until the fifth year, normal growth thereafter may be possible even at current levels of socioeconomic development." (6) Children from the elite groups in developing countries have a growth pattern closer to the National Center for Health Statistics' reference than to the poor of their ethnically similar peers. Thus, the stature of young children in the developing world is more a reflection of poverty than genetics, whereas, in developed countries, genetics plays a greater role. "The growth potential from children around the world is remarkably similar under conditions of adequate nutrition and health." It is the "poverty trap" that prevents the full genetic potential from expression. Not only wasting but also stunting has a positive correlation with childhood mortality and childhood morbidity in that infections are prolonged. There is a close circular relationship between the heights of children and adults in a population and the community's socioeconomic development.

In the last chapter of *Linear Growth Retardation*, Dr Copalan states "There may be academic debates as to what stunting per se does or does not do, but there can be no two opinions about the need for eradication of poverty, which automatically implies the eradication of stunting as well."

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The Editorial Board Speaks . . .

Richard W. Blumberg, MD



Dick has been with us since I assumed the editorship of *AJDC*. He has provided keen insight, interesting suggestions, and the wisdom of his long experience in pediatrics, pediatric education, and medicine in general. His retirement has been a most active one. In this issue, Dick presents us with a viewpoint and perspective on the house call. Many of us recall, in our youth (many, many moons ago for some of us), the attention we received as we went through measles, mumps, varicella, and the other afflictions of childhood. A kindly (usually) family physician would attend us at home, in the comfort of our bedrooms, surrounded by familiar objects and loving relatives. It was a different era, a "kinder, gentler" time, to steal a phrase. However, there was less that the physician could do, little need for elaborate equipment or trained personnel, and many other factors that argued for a change to office-based visits as society and medicine changed. Dr Blumberg's observations are cogent for our times.

THE HOUSE CALL—IS IT AN ANACHRONISM THAT HAS SEEN ITS DAY?

During World War II there was a shortage of physicians to serve the civilian population, including pediatricians and general practitioners. This resulted in the beginning of the trend to "bring the child to the office," producing an end to house calls by the 1950s and early 1960s. Apparently, children did not suffer as a consequence, and during the continuing period of physician shortage the practice persisted, since one could see many more children in the office if house calls were not made. While the physician shortage resolved, the custom has continued.

With the renewed interest in home care for the elderly, one is reminded of that era in which pediatricians made house calls. This is a phenomenon that is completely unknown to modern-day pediatricians, and, thus, it might be postulated that for the past 30 years they have not made house calls. Is this good, a custom that should remain archaic and dead not to be renewed? What are the advantages and disadvantages of house calls?

Advantages

1. Patients are seen in their normal environment.
2. The illness, usually associated with fever, is not aggravated by climatic conditions.
3. The physician can be his or her own social service worker and observe environmental conditions in the home.
4. The washing of hands, either in the kitchen or bathroom, provides the opportunity to counsel parents about substances that are potentially dangerous to small children.
5. If there are other children, they also can be examined if the index case would indicate this is necessary.
6. The parent does not have to find someone to stay with the other children while he or she takes the sick one to the physician. This is, of course, in the event there are other children.
7. Transportation is not a problem for the parent.
8. If the mother works and the child is not in a day-care center, she won't have to go home first to take the child to the physician's office. She can meet him or her at home.
9. Seeing the child at home prevents exposure to other children in the physician's office.
10. The child is usually less upset when seen in the home environment.
11. There is less need to prescribe medication over the telephone in the event the parent is unable to bring the child to the physician's office.

12. The physician's willingness to make an occasional house call makes the parent more willing to come to the office on other occasions.

13. The parents are reassured of the physician's availability.

14. An office nurse might make follow-up visits.

Disadvantages

1. The time spent making house calls is not cost-efficient. It takes too much time traveling, combating traffic, and, in some instances, even finding a place to park.

2. Most children are not too ill to be brought to the office, regardless of the weather.

3. More children can be seen with more time allotted if they are brought to a central location.

4. The cost may be less.

5. Diagnostic procedures may be needed that cannot be done at home (ie, chest roentgenography and certain diagnostic laboratory procedures).

An extreme example of home visitation by a pediatrician involved a most unusual but excellent Cincinnati, Ohio, pediatrician who had no office and saw all of his patients in their home, sick or well. Early in the morning, parents "called in" and he made up his itinerary. Most of the patients had scales and measuring rods, and well-child care, including development, was carefully recorded. Immunizations were given at home. In this setup, there was practically no overhead, no secretaries, rent, office, equipment, etc. Therefore, it was not necessary to see large numbers of patients for economic survival.

Will house calls remain archaic? Probably! Perhaps the *Wall Street Journal* (vol CCXIII, 94, May 15, 1989) had the last word on this subject as the following poem illustrates:

Aches and Pains

My doctor makes house calls;
His charges are meager;
His manner is winning;
His patients are eager.
They line up in cadres
For his benediction—
And what I am writing
is sheer science fiction.

Robert Gordon

Growth Hormone Treatment in Children With Sporadic Primary Microcephaly

Gian Luigi Spadoni, MD; Stefano Cianfarani, MD; Sergio Bernardini, MD; Vaccaro Fabrizio, MD; Cinzia Galasso, MD; Brunetto Boscherini, MD

• Four children with sporadic primary microcephaly associated with short stature, delayed bone age, and low growth velocity are described. All of the children showed a normal growth hormone response to standard pharmacological tests but one of the patients had a reduced spontaneous growth hormone nocturnal secretion. Regardless of the results of their somatotrophic function evaluation, the patients were treated with exogenous growth hormone and all of them showed an increase in growth rate.

(AJDC. 1989;143:1282-1283)

Somatic growth is often impaired in children with primary microcephaly.^{1,2} The reason for the high degree of association between small head circumference and growth failure is unknown, but abnormalities of growth hormone (GH) secretion have been reported in some of these children.³

See also pp 1269, 1284, and 1287.

We studied four prepubertal children with sporadic primary microcephaly associated with severe growth retardation and treated them with exogenous GH regardless of the results of their somatotrophic function evaluation.

PATIENTS AND METHODS

The three boys and one girl were prepubertal throughout the duration of the study. Their ages were between 5.0 and 10.7 years. They all had a height of less than -2.5 SDs from normal, delayed bone age, and a growth rate of less than the 10th percentile for bone age. The patients' head circumferences were less than 2 SDs from normal for height age, and they had no anatomic abnormalities other than a small cranium. They had normal

karyotypes, normal neurologic examination results, subnormal mental development, normal cranium roentgenograms except for reduced diameters, normal gestation periods, normal birth weights (except one patient whose birth weight was 2150 g at term), and normal perinatal periods. The auxological data for each patient are shown in Table 1.

Patients' heights were determined on a wall-mounted stadiometer and are expressed as the mean of at least two measurements taken separately by two observers and not differing by more than 0.4 cm. Height velocity was evaluated for a period ranging from 6 months to 1 year.

Height velocity and pubertal stages were compared with the standards of Tanner and Whitehouse.⁴ Bone age was evaluated according to the Greulich-Pyle method.⁵ Head circumference SDs were calculated by plotting the measurements on interracially and internationally applicable head circumference graphs.⁶

None of the children exhibited any sign of malnutrition, hypothyroidism, malabsorption, or any other evident cause for growth retardation. All of the children underwent provocative testing for GH (arginine, 500 mg/kg intravenously, and clonidine, 75 µg/m² of body surface orally). A 12-hour nocturnal spontaneous GH-secretion assessment was also carried out in all of the children: a catheter was inserted into an antecubital vein and 1 mL of blood was drawn every 30 minutes between 8 PM and 8 AM (25 samples).⁷ The insulin-like growth factor 1 concentration was determined on the last sample.

Serum GH levels were measured using a commercial radioimmunoassay kit (hGH Ter-kit, Biodata, Switzerland) and insulin-like growth factor 1 concentrations were de-

termined by a radioimmunoassay kit from the Nichols Institute, Los Angeles, Calif.

After a pretreatment observation period that lasted at least 12 months, the children were treated with biosynthetic GH (Somatotropin, Kabi, Stockholm, Sweden) at a dosage of 0.5 IU/kg per week divided into three intramuscular administrations. This is the dosage generally employed for GH-deficient children. The treatment lasted for a period of 6 months to 1 year. After the completion of therapy, the children were again observed for 6 months.

Informed consent was obtained from the parents of all of the children. Fourteen children with normal growth variants formed a control group for GH nocturnal spontaneous secretion. They all had height between -2 and -2.5 SDs from normal, a normal height velocity (>25th percentile for chronological age), and a familial history positive for short stature or constitutional delay of growth.

RESULTS

Laboratory data for the children with microcephaly and their growth rates before, during, and after GH treatment are summarized in Table 2. As can be seen, all of the children had a normal response (GH peak >10 µg/L) to one or both pharmacological tests. Three patients had a normal mean 12-hour nocturnal GH concentration (normal values of the 12-hour nocturnal mean concentration are >4 µg/L) while one child had a decreased value (1.7 µg/L). Mean GH nocturnal concentrations in the control group ranged from 3.9 to 12.4 µg/L. The lower limit for the normal range of the

Table 1.—Auxological Data of Patients

Sex	Age, y	Height, cm (SD)	Weight, kg	Bone Age, y	Cranium Circumference, cm	Birth Weight, g
M	5.0	96.4 (-2.5)	14.500	3.5	46.0	2150
M	8.3	110.2 (-3.2)	16.100	7.0	48.5	3600
M	8.3	108.5 (-3.5)	16.500	6.0	47.5	2800
F	10.7	121.5 (-2.5)	25.000	8.8	48.0	3200

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Table 2.—Laboratory Data of the Children and Their Growth Rates Before, During, and After GH Treatment*

GH Peak After Pharmacological Stimulation, $\mu\text{g/L}$		Mean 12-h GH Secretion, $\mu\text{g/L}$	Insulin-like Growth Factor 1, IU/mL	Growth Rate, cm/y (SD)			Increase, cm/y	Treatment, mo
Arginine	Clonidine			Before Treatment	During Treatment	After Treatment		
30.0	34.7	1.7	0.53	4.8 (–1.5)	6.8	4.5	+2.0	9
9.0	14.9	5.0	0.19	2.9 (–3.0)	5.9	2.3	+3.0	12
14.6	7.4	7.5	0.37	2.4 (–3.9)	5.8	3.7	+3.4	6
22.5	10.0	6.5	0.36	3.0 (–2.2)	5.3	3.2	+2.3	12

*GH indicates growth hormone.

mean 12-hour nocturnal GH concentration is in accordance with other studies.⁷⁻⁹

In only one patient were the insulin-like growth factor 1 values subnormal and they were as low as values generally found in GH deficiency. During treatment the growth rate increased in all patients (the increase in height velocity ranged from +2.0 to +3.4 cm/y) and decreased after withdrawal of GH. Treatment was well tolerated and no adverse effects were observed. A significant negative correlation was found between pretreatment growth velocity (expressed as SD for chronological age) and the increase in height velocity ($r = .99$; $P > .01$).

COMMENT

Pharmacological tests showed a normal GH response in the four children so none of them could be diagnosed as having a "classic" GH deficiency. But one of the patients showed a reduced spontaneous 12-hour GH secretion. Also, other patients with primary microcephaly have been described with reduced GH spontaneous secretion.⁸

All of the children responded to therapy with an increase in growth velocity. An increase of more than 2 cm/y is considered satisfactory by various authors^{10,11}; using this criterion all of the children in this study showed a satisfactory response to GH therapy. The poorest response was shown by the patient who, theoretically, was expected to respond best since he had a reduced spontaneous GH secretion. However, we should also consider that this child was small for gestational age at birth, and the possibility of false-positive results of his spontaneous GH secretion evaluation cannot be excluded.

There is a significant negative correlation

between pretreatment growth velocity and its increase during treatment. These data are also described for normal variants of growth and for GH-deficient children. Thus, height velocity seems to be a useful indicator in predicting the response to therapy and might be a good tool to select non-GH-deficient children to be treated with GH.¹²⁻¹⁴

Our data do not help establish the causes of growth retardation in children with primary microcephaly, but they do suggest that some children with this condition in whom no evident cause for growth retardation has been found may respond to GH therapy if evaluation of somatotropic function has not revealed a GH deficiency. Careful assessment is obviously needed to establish a risk-benefit ratio for the use of GH in children with microcephaly and short stature as in all other non-GH-deficient children.

It must be pointed out that the treatment period in our study was short, and it is not known if the accelerated growth would be sustained with long-term treatment or if the eventual height of these children will be sufficiently improved to justify this demanding and costly treatment. Also, in the case of the carefully controlled long-running studies being carried out in other short non-GH-deficient children (as in girls with Turner's syndrome), the final word is not yet in as to how much improvement there will be in the final height.¹⁵

We employed the same dosage of GH as is generally used for GH-deficient children, but the employment of higher dosages could also be considered. In children with Turner's syndrome, doubling the dosage of GH (from 0.5 to 1 IU/kg per week) has been demonstrated to result in significantly greater height velocity increases with no differ-

ence in advancement of bone age.¹⁶ Obviously, even more careful attention to side effects would be required for such a high-dosage therapeutic regimen.

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Diagnostic Limitations of Spontaneous Growth Hormone Measurements in Normally Growing Prepubertal Children

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• To evaluate whether the measurement of the spontaneous overnight growth hormone secretion in prepubertal children clearly separated normal children from subjects with growth hormone deficiency, we studied 45 prepubertal normally growing children (10 with normal height and 35 with constitutional growth delay) and compared their overnight growth hormone secretion with that of a group of subjects with either isolated growth hormone deficiency or neurosecretory dysfunction. Peak growth hormone levels (≥ 10 ng/mL) following oral clonidine administration were normal in individuals with normal height, constitutional growth delay, and neurosecretory dysfunction, as was the basal somatomedin C concentration; subjects with growth hormone deficiency had low peak growth hormone levels (< 10 ng/mL) following oral clonidine administration as well as low basal somatomedin C values. The mean 9-hour overnight growth hormone concentration, total growth hormone output, total number of nocturnal pulses, and the mean peak growth hormone response during nocturnal sampling were similar in the normal height and constitutional growth delay groups and significantly greater than those seen in subjects with either growth hormone deficiency or neurosecretory dysfunction. Twelve (26.6%) of 45 normally growing children (4 of 10 normal height and 8 of 35 constitutional growth delay), however, had low overnight growth hormone levels (< 3 ng/mL), which overlapped results obtained in the growth hormone-deficient or neurosecretory dysfunction groups. Frequent overnight growth hormone (GH) sampling does not always separate normal-growing children from those with partial or com-

plete GH deficiency. In our this study over one quarter of the normally growing children had overnight GH levels in the range of children with either GH deficiency or neurosecretory dysfunction. These findings, in addition to the cost and difficulty in performing this test, do not support the measurement of spontaneous GH as a routine test in short but normally growing prepubertal children.

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Several articles have suggested that frequent GH sampling over 24 hours or during sleep may be a more clinically relevant assessment of the GH secretory status of a child than the GH response to pharmacologic stimuli.¹⁻³

See also pp 1269, 1282 and 1287.

According to these studies, GH stimulation tests frequently do not reflect the endogenous GH secretion, so that some individuals with normal responses to these tests have a reduced spontaneous secretion of GH and may benefit from treatment with GH.

A recent study,⁴ however, found that the measurement of the spontaneous secretion of GH in prepubertal short children had lower sensitivity and offered no diagnostic advantage over stimulation tests in the diagnosis of GH deficiency.

While studying the overnight GH levels of a control group of normal-height children, we noticed that an appreciable number of their GH values seemed to overlap with those of short children, including those with classical GH deficiency. This prompted us to determine whether we could clearly separate normally growing prepubertal children from those with GH deficiency or neurosecretory dysfunction relying primarily on their spontaneous overnight GH secretion, using 3 ng/mL as a cutoff

point in separating these groups as has been suggested by several studies in children.^{5,6}

METHODS

Forty-five apparently healthy normally growing (≥ 5 cm/y) prepubertal children (34 boys and 11 girls) with a mean (\pm SD) chronologic age of 8.7 ± 2.3 years (range, 6 to 12 years) were studied at the pediatric endocrine clinic of the Hospital Central "Dr Carlos Arvelo." Thirty-five of these subjects were growing at below the fifth percentile for height but maintaining a normal growth velocity (≥ 5 cm/y), and their bone ages were equal to or greater than 2 years delayed compared with their chronologic ages.

The remaining 10 normal-height children (8 boys and 2 girls) had a mean chronologic age of 10.3 ± 2.7 years (range, 7 to 13 years) and were growing adequately (≥ 5 cm/y) above the 10th percentile (range, 25th to 75th percentiles) for height, and had bone ages similar to their chronologic ages. All subjects had appropriate body weight for height.

Normal complete blood cell counts, erythrocyte sedimentation rates, routine blood chemistry study results, and thyroid function test results were obtained prior to GH testing in all patients and controls. Bone ages were determined by hand films according to the method of Greulich and Pyle.⁷

After an overnight fast, all patients received a single oral dose of $100 \mu\text{g}/\text{m}^2$ of clonidine early in the morning, and blood samples for GH determination were drawn in a recumbent position at 0, 60, and 90 minutes thereafter; blood pressure was measured every half hour. In addition, a single plasma specimen was obtained at the time of initial sampling for measurement of somatomedin C. For the GH-release studies during sleep, blood samples were drawn from an indwelling venous catheter every 30 minutes from 9 PM until 6 AM.

Patients were admitted 4 hours before the overnight sampling and had a balanced dinner at 6 PM. An effort was made to avoid stress and to encourage normal activity during this period. Lights were turned off at 9 PM, and each patient's status was recorded

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as awake or asleep; all patients had a minimum of 7 hours of observed sleep. The nocturnal study was begun on the same day, or a few days after, the clonidine was given.

Samples were stored at -20°C . Specific radioimmunoassay techniques were used for the determination of serum GH using chemically prepared human GH double-antibody radioimmunoassay (RIA Kits, Diagnostic Products Corp, Los Angeles, Calif) as previously described.⁸ All samples were assayed in duplicate by the same laboratory technician. Blood for SMC determination was collected in ethylenediaminetetraacetic acid tubes, and plasma was frozen and shipped to Nichols Institute in Los Angeles for SMC radioimmunoassay.

Growth hormone concentrations equal to or greater than 10 ng/mL after subjects took oral clonidine were considered normal. Integrated overnight GH concentrations were determined by obtaining the mean of all measurements for each child. We arbitrarily considered that a minimum GH pulse must exceed 5 ng/mL. Comparison of integrated overnight GH concentrations and of basal SMC levels of the population studied was accomplished by ANOVA. Total GH output was estimated by measuring the area under the curve vs a 9-hour time curve, and comparison of both groups was done with the unpaired *t* test and the Mann-Whitney *U* Test. Results are expressed as mean \pm SD.

Results of our patients' GH testing were compared with those of a group of seven children with isolated GH deficiency (6 boys and 1 girl; chronologic age, 9.1 ± 3.5 years), serum GH response to at least two different provocative tests of less than 10 ng/mL, growth velocity of less than 4 cm/y, delayed skeletal age, low plasma somatomedin C level, and low mean 9-hour overnight GH concentrations (<3 ng/mL) (Table); and with those of a group of seven children with neurosecretory dysfunction (6 boys and 1 girl; chronologic age, 10.3 ± 3.1 years), growth velocity of less than 4 cm/y, delayed skeletal age, peak serum GH response to one or more provocative tests of equal to or greater than 10 ng/mL, and low mean 9-hour overnight GH levels (<3 ng/mL) (Table).

The studies were performed with the approval of the hospital research and publications committee, and with informed parental consent.

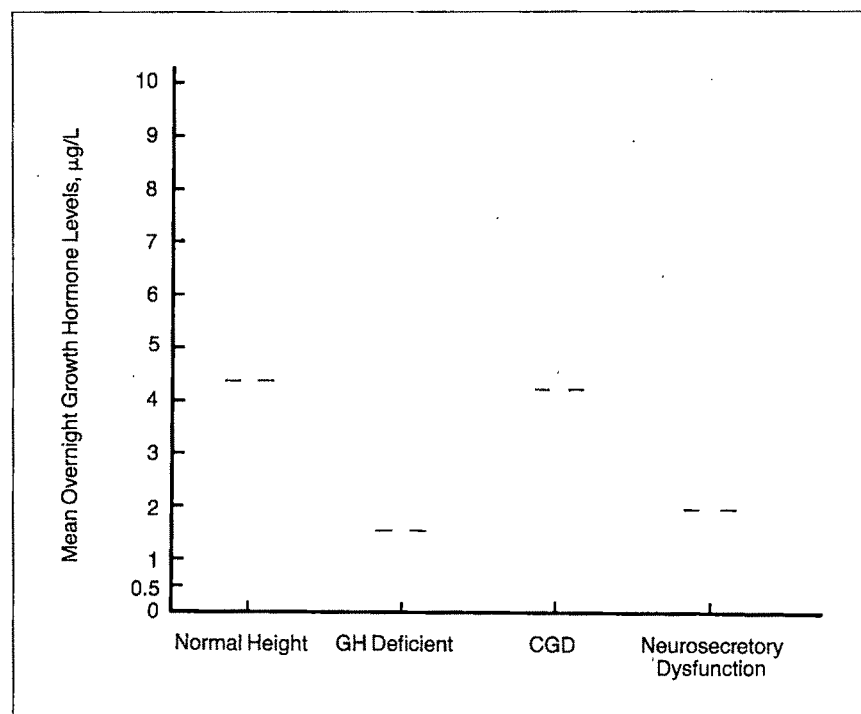
RESULTS

All 45 normally growing subjects as well as all patients with neurosecretory dysfunction were able to increase their GH levels to equal to or greater than 10 ng/mL after oral clonidine ingestion. Mean peak GH concentrations of 22.0 ± 8.3 ng/mL, 17.8 ± 6.7 ng/mL, and

Group	Mean Overnight GH Levels, $\mu\text{g/L}$	Total Basal GH Output, U†	Total Nocturnal GH Pulses, ng/mL	Mean Peak Nocturnal GH Level, ng/mL
Children with constitutional growth delay	4.2 ± 1.8	224 ± 92	3.5 ± 0.7	13.0 ± 1.2
Normal-height children	4.4 ± 2.8	222 ± 135	3.3 ± 1.3	13.2 ± 1.3
Children with neurosecretory dysfunction	2.0 ± 0.4	41 ± 5	1.9 ± 0.4	9.0 ± 1.3
Children with GH deficiency	1.6 ± 0.2	25 ± 6	1.8 ± 0.4	5.2 ± 1.1

*Values are expressed as mean \pm SD. GH indicates growth hormone.

†Total GH output was estimated by measuring the area under the curve vs a 9-hour time curve.



Mean overnight growth hormone (GH) levels in normal-height children, children with constitutional growth delay (CGD), and children with GH deficiency and neurosecretory dysfunction. The solid lines represent the average value in each subject group.

16.8 ± 5.3 ng/mL were obtained by the normal height, constitutional growth delay (CGD), and neurosecretory dysfunction groups, respectively, 60 minutes after oral clonidine ingestion. Mean peak GH levels were 4.1 ± 1.2 ng/mL in the GH-deficient group after clonidine stimulation. Basal somatomedin C levels were 1.0 ± 0.5 U/mL, 1.1 ± 0.3 U/mL, and 1.0 ± 0.4 U/mL in the normal-height children, those with CGD, and in subjects with neurosecretory dysfunction, respectively. The mean somatomedin C level in the GH-deficient children was significantly reduced compared with the other three groups (0.4 ± 0.1 U/mL; $P < .01$).

Mean 9-hour overnight GH concentrations, total basal GH output, number of nocturnal GH pulses, and mean peak GH response during nocturnal sampling of normal-height children and subjects with CGD were similar and significantly larger than those seen in the groups with neurosecretory dysfunction and GH deficiency ($P < .001$) (Table and Figure).

However, 12 (26.6%) of 45 normally growing children had low mean 9-hour overnight GH levels, so that 4 (40%) of 10 normal-height children and 8 (22.9%) of 35 subjects with CGD had mean 9-hour overnight GH concentrations of less than 3 ng/mL, which overlapped

with levels obtained in the 7 patients with neurosecretory dysfunction and in 7 GH-deficient subjects (Figure).

COMMENT

Several recent reports^{5,6} have suggested that in addition to clinical findings and GH provocative testing, a mean 24-hour or overnight GH level of 3 ng/mL could be used as a cutoff point in separating normally growing children (≥ 3 ng/mL) from those with classical GH deficiency or neurosecretory dysfunction (< 3 ng/mL).

In this study we considered both normal-height children and children with CGD as part of a healthy normal group, since subjects in both these groups were growing normally at equal to or greater than 5 cm/y and since in a previous report we were unable to find any difference in the mean GH secretion of children with CGD and that of a normal-height control population when we evaluated their GH response to provocative testing, their spontaneous overnight GH secretion, and their basal somatomedin C levels.⁸ Similar results have recently been reported by Rose et al.⁴

We found that 12 (26.6%) of the 45 normally growing children had a mean overnight GH concentration less than 3 ng/mL, overlapping with values obtained by patients with GH deficiency and neurosecretory dysfunction. These low GH levels were detected in a fair number of both normal-height and CGD children (40% and 22.9%, respectively). By using overnight GH sampling as the

sole means of evaluating the GH status of normally growing children, over one quarter of this population would have been considered to have some form of GH deficiency (partial or complete).

We only evaluated overnight GH levels since the diagnostic validity of overnight GH sampling has been confirmed by several recent reports,^{4,6,9} which, based on the excellent correlation between overnight and 24-hour GH concentrations, suggested that overnight testing could substitute for 24-hour sampling for most diagnostic purposes.⁶

In this study we limited ourselves to studying the spontaneous GH secretion of a group of prepubertal children. We do not know whether pubertal subjects, in whom sexual hormones have been shown to increase spontaneous secretion of GH,^{10,11} will also show a significant overlap in GH levels sampled frequently. Both obesity and depression are factors known to decrease the 24-hour integrated GH concentrations⁶; however, all of our patients were healthy, came, as far as we could tell, from stable environments, and had an appropriate body weight for height.

Frequent GH sampling is apparently not as sensitive as provocative testing in the diagnosis of GH deficiency,⁴ and, as shown in this study, if it is used as the only laboratory tool for determining the GH status of individual short but normally growing children, it can give an appreciable number of false-positive results.

In addition, Donaldson et al⁹ recently reported that a single overnight GH se-

cretory profile may not reflect physiological GH production, as significant variation in GH secretory profiles on consecutive nights was found. All of these data, compounded by the cost and difficulty in performing this test, do not support the measurement of spontaneous GH as a routine diagnostic test in prepubertal children.

Both provocative testing and measurement of the spontaneous GH levels in prepubertal children have been shown to have a margin of error. It is known that normal subjects may not respond to any single stimulus for GH: Penny et al¹² found that 20% of normal subjects did not respond to arginine and 20% did not respond to insulin, and my colleagues and I¹³ found a lack of response to exercise in 11.9% of normal children. This study demonstrates how over 25% of normally growing prepubertal children may have low spontaneous overnight GH levels.

It may be concluded that no one testing procedure for GH secretion alone, direct (overnight secretion, 24-hour integrated secretion, provocative stimuli testing) or indirect (somatomedin C), is able to identify the individual who is GH deficient. Only when the testing procedures are combined with a growth rate that is less than the minimal normal growth rate per year can the individual who is GH deficient be identified. Additionally, it should be noted that a satisfactory assessment of a child's growth cannot be made over a period of less than 1 year.

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Criteria for Recognition of the Growth-Inefficient Child Who May Respond to Treatment With Growth Hormone

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• In this study three groups of short children composed of 104 subjects (61 boys, 43 girls) were evaluated for spontaneous secretion of growth hormone (GH). Group 1 consisted of 10 subjects (6 boys, 4 girls) with "classic" GH deficiency. Group 2 consisted of 31 subjects (17 boys, 14 girls) with "nonclassic" GH deficiency. Group 3 consisted of 63 subjects (38 boys, 25 girls) with short normal stature. Blood samples were drawn every 20 minutes over 24 hours, and the mean GH concentration, nocturnal GH concentration, diurnal GH concentration, pulse amplitude, and number of pulses with a GH peak above 5 $\mu\text{g/L}$ were determined. The values for mean height, height velocity, bone age to chronological age ratio, somatomedin C concentration, GH concentration, nocturnal GH concentration, diurnal GH concentration, pulse amplitude, and number of pulses with a GH peak over 5 $\mu\text{g/L}$ were significantly greater in group 3 than in group 2, and these same values, except for the mean diurnal GH concentration, were greater in group 2 than in group 1. The mean GH concentration correlated with the mean nocturnal GH concentration. Subjects in groups 1 and 2 were treated with GH for 1.23 ± 0.53 years (mean \pm SD). All the group 1 subjects and 27 (87%) of the group 2 subjects responded with an increase in height velocity greater than 2 SDs per year of therapy. In conclusion, 87% of subjects with a normal GH response to provocative stimuli testing who had a mean height velocity of less than 4 cm/y, mean height lower than the third percentile, mean bone age to chronological age ratio of less than 0.8, and mean GH concentration less than 3 $\mu\text{g/L}$ responded to GH therapy.

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Until recently, treatment of short children with growth hormone (GH) has been limited to subjects with an im-

See also pp 1269, 1282, and 1284.

paired height velocity (HV) and unequivocal GH deficiency demonstrated by blunted responses on at least two

provocative stimuli tests ("classic" GH deficiency).¹

The availability of virtually unlimited supplies of biosynthetic GH offers the physician new therapeutic perspectives.^{2,9} Indeed, in the last few years, many short children who did not fulfill the rigid criteria of GH deficiency have been treated with GH, and in many but not all instances an increased HV has been obtained.¹⁰⁻²⁵

Growth hormone is a potent agent with a variety of important metabolic actions,³ and some adverse effects may occur during GH administration, especially in children without GH deficiency.^{2,3,26,27} Because ethical and economical issues also have to be taken into account, the problem of how to select short children for GH treatment is still unresolved.¹⁸ Moreover, a short-term increase in HV does not necessarily result in an improvement in long-term growth, with an increased adult height.^{8,9,20,28} When the expectation of a taller height is not reached, children and parents may become psychologically discouraged. Therefore, a detailed investigation of short children who are potentially able to respond to GH therapy with improved linear growth is advocated.

Recent studies have dealt with the usefulness of the evaluation of spontaneous GH secretion as a very sensitive approach in diagnosis for short children.²⁹⁻³⁷ Nevertheless, in the opinion of some, this procedure has less diagnostic accuracy than conventional provocative GH testing.³⁸

In the present study we evaluate whether short children with subnormal spontaneous GH secretion may benefit from GH therapy and whether there is a relationship between the 24-hour mean GH concentration and other hormonal measurements or auxologic features.

PATIENTS AND METHODS

Patients

One hundred four (61 boys, 43 girls) growth-retarded but otherwise healthy children with normal birth weight and length

were selected for the study; their chronological age (CA) at the time of evaluation was 8.89 ± 1.68 years (mean \pm SD).

Height (mean of three measurements using a wall-mounted stadiometer), weight, and HV (evaluated during the year before the examination) were evaluated. Bone age (BA) and predicted adult height were determined according to the method of Tanner et al.³⁹ To allow a comparison between different ages and between sexes, height and HV were expressed as SD scores: $(x - \bar{x})/\text{SD}$, where x is the observed value, \bar{x} is the mean value of height and HV for CA and BA, respectively, and SD is the standard deviation for CA and BA, respectively, using the standards of Tanner et al.^{40,41} Height age (HA) was also evaluated according to the methods of Tanner et al.⁴⁰

Auxologic features were considered "pathologic" if HV was more than 1.5 SDs below normal and the BA/CA ratio was lower than 0.8; auxologic features were considered "nonpathologic" if HV was less than 1.5 SDs below normal and the BA/CA ratio was greater than 0.8.

The height of all subjects was more than 1.8 SDs below normal (2.35 ± 0.39 SDs below normal). Weight results were within 1 SD of the mean for height age.⁴⁰ The children were selected to examine mainly subjects with pathologic auxologic features; therefore, 84 children with pathologic auxologic features (HV: 3.86 ± 0.65 cm/y, 2.36 ± 0.64 SDs below normal; BA/CA ratio: 0.72 ± 0.06) and 20 children with nonpathologic auxologic features (HV: 4.55 ± 0.45 cm/y, 1.32 ± 0.44 SDs below normal; BA/CA ratio: 0.94 ± 0.05) were enrolled in the study. Psychosocial deprivation syndrome and other endocrine or nonendocrine systemic diseases were ruled out. Results of the karyotype examination, carried out in all girls, were normal. At the time of the 24-hour study, pubertal staging ranged from prepubertal to stage II, according to the criteria of Tanner.⁴²

The study was approved by the Ethical Committee of the Medical Faculty, University of Pisa, Italy. Informed consent for the study was obtained from parents and any child over 12 years old.

All children underwent two pharmacologic stimuli tests, levodopa administration (500 mg per 1.73 m^2) and the insulin tolerance test (0.1 U of regular insulin per kilogram intravenously). Blood samples were drawn for GH measurement every 20 minutes for 2 hours during both tests. During the insulin tolerance test, adequate hypoglycemia, ie, blood

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glucose levels less than half the basal level and/or lower than 2.2 mmol/L, was achieved in all children.

Serum somatomedin C/insulinlike growth factor I was evaluated four times at 8 AM at monthly intervals⁴³ and expressed as a mean value.

24-Hour GH Evaluation

The children were admitted on the day before the spontaneous GH evaluation, which consisted of drawing 1 mL of blood through an indwelling intravenous catheter (placed in a forearm vein 1 hour before beginning the study) every 20 minutes over 24 hours (from 8 AM to 8 AM of the following day). Subjects were fed at 7 AM, 12 PM, 4 PM, and 8 PM and were encouraged to continue their normal activities, such as walking, playing, or reading.

All 73 samples were measured for each child, and the following secretory measurements were evaluated: (1) 24-hour mean GH concentration, the arithmetic mean of all 73 values; (2) nocturnal 12-hour mean GH concentration, the arithmetic mean of 37 samples from 8 PM to 8 AM of the following day; (3) diurnal 12-hour mean GH concentration, the arithmetic mean of 37 samples from 8 AM to 8 PM; (4) number of pulses with a GH peak greater than 5 µg/L; and (5) mean pulse amplitude, the arithmetic mean of all GH peaks greater than 1.5 µg/L.

GH Therapy

No child had received previous hormonal treatment.

Subjects with a mean GH concentration lower than 3 µg/L were treated with GH, 12 IU/m² per week, divided into three subcutaneous injections. During GH therapy, height, weight, HV, and BA were evaluated every 6 months, while the following values were determined every 3 months: glycemia, transaminases, cholesterol, triglycerides, white blood cell counts, thyroxine, and thy-

rotropin. The change of auxologic features during GH therapy have been expressed as the change in the SD score for height, the change in HA, the ratio of the change in HA to change in CA ($\Delta HA/\Delta CA$), the change in the SD score for HV, the ratio of the change in HA to the change in BA ($\Delta HA/\Delta BA$), and the change in predicted adult height; some of these have also been expressed as the change per year to allow a comparison between different periods of GH therapy.

Hormonal Assays

All 73 samples of the 24-hour evaluation for every child were measured in duplicate for GH in one assay by a two-site immunoradiometric assay using two different antibodies in excess (Pharmacia Diagnostics AB, Uppsala, Sweden). The within-assay and total-assay coefficients of variation for GH values were 2.5% to 5.1% and 3.5% to 5.6%, respectively. Cross-reactivity was less than 1% for human placental lactogen and prolactin. The sensitivity of the GH assay was 0.2 µg/L; values below 0.25 µg/L were considered to be 0.25 µg/L.

Somatomedin C levels were determined

by a radioimmunoassay kit (Diagnostic Systems Laboratories Inc, Webster, Tex). The sensitivity was 8 IU/L, while the cross-reactivity was 8% for insulinlike growth factor II. The intra-assay and the interassay coefficients of variation were 2.7% to 9.2% and 7% to 10%, respectively.

Statistical Analysis

The statistical methods used to analyze the hormonal data and auxologic features were Student's *t* test for paired and unpaired subjects and linear regression analysis.

RESULTS

The subjects were subdivided into three groups according to their GH responses to provocative stimuli testing (Table 1) and their mean GH concentration. Group 1 consisted of 10 subjects (6 boys, 4 girls) who had a diagnosis of classic GH deficiency on the grounds of two provocative stimuli test results that included a peak GH concentration lower than 10 µg/L and pathologic auxologic features; the mean GH concentration

Table 1.—Hormonal Data of Examined Children*

Group	No. of Patients		Growth Hormone, µg/L		
			Insulin Tolerance Test	Levodopa Administration	Somatomedin C, IU/L
1	10	Mean ± SD	3.3 ± 1.4	3.0 ± 1.9	270 ± 100
		Range	0.5-5.7	0.9-6.5	120-410
2	31	Mean ± SD	14.0 ± 7.8	13.6 ± 6.6	460 ± 160
		Range	2.3-30.8	2.6-25.4	210-750
3	63	Mean ± SD	15.8 ± 6.3	13.6 ± 7.0	900 ± 380
		Range	4.2-27.1	2.0-25.9	250-2330

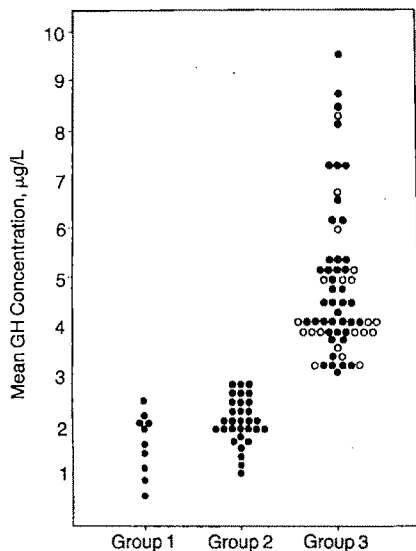
*For group 1 vs group 2, *P* < .001 for the insulin tolerance test and levodopa administration, *P* < .002 for somatomedin C; group 1 vs group 3, *P* < .001 for the insulin tolerance test, levodopa administration, and somatomedin C; and group 2 vs group 3, *P* was not significant for the insulin tolerance test and levodopa administration and *P* < .001 for somatomedin C. For the insulin tolerance test vs levodopa administration, *P* was not significant in all the groups.

Table 2.—Spontaneous Growth Hormone Study of Examined Children*

Group	No. of Patients		Growth Hormone Concentration, µg/L			No. of Pulses With a Growth Hormone Peak > 5 µg/L	Mean Pulse Amplitude, µg/L
			Mean	Nocturnal	Diurnal		
1	10	Mean ± SD	1.66 ± 0.62	1.94 ± 0.65	1.38 ± 0.61	0.30 ± 0.48	3.57 ± 1.24
		Range	0.61-2.04	0.92-2.16	0.30-1.99	0-1	1.79-5.04
2	31	Mean ± SD	2.14 ± 0.46	2.65 ± 0.75	1.62 ± 0.56	2.13 ± 0.88	5.41 ± 1.72
		Range	1.08-2.87	1.12-4.16	0.94-2.70	1-4	2.16-9.64
3	63	Mean ± SD	4.89 ± 1.54	5.92 ± 1.88	3.87 ± 1.42	5.24 ± 1.63	10.82 ± 2.76
		Range	3.07-9.57	3.16-11.02	0.68-8.56	1-8	5.92-14.46

*For group 1 vs group 2, *P* < .02 for mean growth hormone concentration and mean nocturnal growth hormone concentration, *P* was not significant for mean diurnal growth hormone concentration, *P* < .001 for number of pulses with a growth hormone peak greater than 1.5 µg/L, and *P* < .005 for mean pulse amplitude; group 1 vs group 3, *P* < .001 for all measurements; and group 2 vs group 3, *P* < .001 for all measurements. For mean growth hormone concentration vs mean nocturnal growth hormone concentration, *P* was not significant for group 1, *P* < .005 for group 2, and *P* < .001 for group 3. For mean growth hormone concentration vs mean diurnal growth hormone concentration, *P* was not significant for group 1 and *P* < .001 for groups 2 and 3. For mean nocturnal growth hormone concentration vs mean diurnal growth hormone concentration, *P* was not significant for group 1 and *P* < .001 for groups 2 and 3.

was lower than 3 $\mu\text{g/L}$. Group 2 consisted of 31 subjects (17 boys, 14 girls) with a diagnosis of nonclassic GH deficiency; they had a normal response (peak GH concentration $>10 \mu\text{g/L}$) to levodopa administration and/or an insulin tolerance test (13 subjects responded to both tests; 18 responded to one test)



Twenty-four-hour mean growth hormone (GH) concentrations in the 104 examined short children. Group 1 ($n=10$) includes children with classic GH deficiency; group 2 ($n=31$), children with nonclassic GH deficiency (peak GH concentration $>10 \mu\text{g/L}$ in response to one or two provocative tests and mean GH concentration $<3 \mu\text{g/L}$); and group 3 ($n=63$), children with short normal stature (peak GH concentration $>10 \mu\text{g/L}$ in response to one or two provocative tests and mean GH concentration $>3 \mu\text{g/L}$). Solid circle indicates short children with a bone age to chronological age ratio lower than 0.8 and a height velocity more than 1.5 SDs below normal; open circle, short children with a bone age to chronological age ratio greater than 0.8 and a height velocity less than 1.5 SDs below normal.

and a mean GH concentration lower than 3 $\mu\text{g/L}$. Group 3 consisted of 63 subjects (38 boys, 25 girls) with a diagnosis of short normal stature; they had a normal response (peak GH concentration $>10 \mu\text{g/L}$) to levodopa administration and/or an insulin tolerance test (26 subjects responded to both tests; 37 responded to one test) and a mean GH concentration greater than 3 $\mu\text{g/L}$.

All the subjects in groups 1 and 2 were prepubertal. Somatomedin C values and peak GH concentrations in response to insulin tolerance tests and levodopa administration in group 1 were significantly lower than those in groups 2 and 3 ($.001 < P < .02$). The only difference between groups 2 and 3 was increased somatomedin C levels in group 3 ($P < .001$).

Results of the spontaneous GH secretion study (mean GH concentration, mean nocturnal GH concentration, mean diurnal GH concentration, number of pulses with a peak GH concentration over 5 $\mu\text{g/L}$, and mean pulse amplitude) of the examined children are reported in Table 2. The individual values for mean GH concentration are shown in the Figure. In all children, the mean diurnal GH concentration was lower than the mean nocturnal GH concentration. All GH measurements in group 2 except mean diurnal GH concentration were significantly greater ($.001 < P < .02$) than those in group 1, whereas all GH values in group 3 were significantly greater ($P < .001$) than those in group 2, so that GH measurements in group 2 were intermediate compared with those in groups 1 and 3.

Furthermore, in groups 2 and 3 but not in group 1, the mean GH concentration was significantly lower than the mean nocturnal GH concentration

($.001 < P < .005$) and significantly greater than the mean diurnal GH concentration ($P < .001$), and, obviously, the mean nocturnal GH concentration was significantly greater than the mean diurnal GH concentration ($P < .001$).

A comparison of auxologic features among the three groups is given in Table 3. In addition to the patients with classic GH deficiency (group 1), all the subjects with nonclassic GH deficiency (group 2) had pathologic auxologic features, while all 20 subjects with nonpathologic auxologic features together with the remaining 43 subjects with pathologic auxologic features (short normal children, group 3) had a mean GH concentration greater than 3 $\mu\text{g/L}$. Values in group 2 were significantly greater ($P < .001$ for SD score for height, $P < .002$ for BA/CA ratio, $P = .002$ for SD score for HV) than in group 1 and significantly lower ($P < .001$ for SD scores for height and HV and for BA/CA ratio) than in group 3. Obviously, values in group 3 were significantly greater ($P < .001$ for SD scores for height and HV and for BA/CA ratio) than in group 1.

The correlations between mean GH concentration and other GH measurements, somatomedin C concentration, and auxologic features were as follows: mean nocturnal GH concentration: $r = .979$, $P < .001$ (linear regression equation: $y = 1.19x + 0.09$); mean diurnal GH concentration: $r = .951$, $P < .001$ ($y = 0.78x - 0.01$); somatomedin C concentration: $r = .794$, $P < .001$ ($y = 0.22x - 0.16$); mean pulse amplitude, $r = .832$, $P < .001$; number of pulses with a GH peak greater than 5 $\mu\text{g/L}$, $r = .637$, $P < .001$; SD score for HV: $r = .499$, $P < .001$; SD score for height: $r = .414$, $P < .001$; BA/CA ratio:

Table 3.—Comparison of Auxologic Features Among Examined Children*

Group	No. of Patients		CA, y	Height		BA, y	BA/CA Ratio	Height Velocity	
				cm	SD Score			cm/y	SD Score
1	10	Mean \pm SD	7.75 \pm 1.49	106.0 \pm 7.5	-3.22 \pm 0.28	4.97 \pm 0.93	0.63 \pm 0.06	3.03 \pm 0.71	-3.26 \pm 0.45
		Range	5.61-9.67	95.1-117.1	-3.55- -2.92	3.98-5.96	0.59-0.71	1.8-3.8	-3.96- -2.83
2	31	Mean \pm SD	8.76 \pm 1.43	115.3 \pm 7.7	-2.44 \pm 0.33	6.23 \pm 1.15	0.71 \pm 0.06	3.73 \pm 0.65	-2.56 \pm 0.60
		Range	6.75-11.83	105.4-131.1	-3.03- -1.87	3.67-8.40	0.54-0.79	2.2-5.1	-4.11- -1.86
3	63	Mean \pm SD	9.16 \pm 1.73	118.8 \pm 8.8	-2.17 \pm 0.18	7.42 \pm 1.65	0.81 \pm 0.10	4.27 \pm 0.46	-1.79 \pm 0.52
		Range	5.83-13.25	101.5-139.0	-2.71- -1.97	4.11-10.33	0.68-1.03	3.4-5.2	-3.08- -0.71

*CA indicates chronological age; BA, bone age. For group 1 vs group 2, P was not significant for CA, $P < .001$ for SD score for height, $P < .002$ for BA/CA ratio, and $P = .002$ for SD score for height velocity; group 1 vs group 3, $P < .02$ for CA and $P < .001$ for SD score for height, BA/CA ratio, and SD score for height velocity; and group 2 vs group 3, P was not significant for CA and $P < .001$ for SD score for height, BA/CA ratio, and SD score for height velocity.

$r = .297$, $P < .02$; peak GH concentration during insulin tolerance test: $r = .290$, $P < .05$; and peak GH concentration after levodopa administration: $r = .232$, P , not significant.

By analysis of the regression equations for the mean GH concentration (x) compared with the mean nocturnal GH concentration (y) and the mean diurnal GH concentration (y), the values that corresponded to a mean GH concentration of $3 \mu\text{g/L}$ were $3.66 \mu\text{g/L}$ for mean nocturnal GH concentration and $2.33 \mu\text{g/L}$ for mean diurnal GH concentration. If we use these values as cutoff points to separate subjects with a "normal" mean GH concentration from those with a "low" mean GH concentration, the specificity and sensitivity⁴⁴ of the nocturnal and diurnal evaluations were as follows: The mean nocturnal GH concentration was normal in 61 of 63 subjects who had a mean GH concentration greater than $3 \mu\text{g/L}$ (specificity, 97%) and pathologic in 38 of 41 subjects with a mean GH concentration lower than $3 \mu\text{g/L}$ (sensitivity, 93%). The mean diurnal GH concentration was normal in 56 of 63 subjects with a mean GH concentration greater than $3 \mu\text{g/L}$ (specificity, 89%) and pathologic in 36 of 41 subjects with a mean GH concentration lower than $3 \mu\text{g/L}$ (sensitivity, 88%).

On the basis of the regression equation for the mean GH concentration and the somatomedin C concentration, the somatomedin C value that corresponded to a mean GH concentration value of $3 \mu\text{g/L}$ was 500 IU/L. The somatomedin C concentration was below 500 IU/L in all children in group 1 (100%), in 19 (61%) of 31 children in group 2, and in 12 (19%) of 63 children in group 3 (only 1 child among those with nonpathologic auxologic features had a somatomedin C concentration below 500 IU/L). The somatomedin C concentration was also highly correlated ($P < .001$) with the SD score for HV ($r = .583$), the SD score for height ($r = .540$), the BA/CA ratio ($r = .447$), and the CA ($r = .344$). The SD score for HV was also correlated with the mean pulse amplitude ($r = .604$, $P < .001$) and the number of pulses with a GH peak greater than $5 \mu\text{g/L}$ ($r = .526$, $P < .001$).

The effects of GH therapy on the 41 treated subjects are shown in Table 4. At the time of this report, 8 subjects had been receiving therapy for 24 months,

Table 4.—Comparison of Auxologic Features							
Group	No. of Patients	Therapy Period, y	Height After Growth Hormone Therapy				
			cm	SD Score	ΔSD Score	ΔSD Score/y	
1	10	Mean±SD	1.25±0.54	116.3±10.0	-2.46±0.37	+0.77±0.27	+0.66±0.19
		Range	.5-2.0	99.7-130.3	-2.91-1.84	0.42-1.10	0.42-1.00
2	31	Mean±SD	1.23±0.53	124.8±6.8	-1.84±0.32	+0.60±0.33	+0.49±0.21
		Range	.5-2.0	109.1-137.5	-2.26-1.50	+0.13-1.24	+0.21-1.24

*HA indicates height age; CA, chronological age; and BA, bone age. $P < .001$ for both groups for SD score for height after growth hormone treatment compared with before growth hormone treatment and for SD score for height velocity during growth hormone treatment compared with before growth hormone

12 subjects for 18 months, 12 subjects for 12 months, and 9 subjects for 6 months (mean \pm SD treatment period, 1.23 ± 0.53 years). No subject had onset of pubertal development during treatment. There was no statistical correlation between the mean GH concentration and the SD score for HV during therapy. The SD scores for both height and HV were significantly higher ($P < .001$) during the treatment period than before treatment in both groups 1 and 2.

Subjects in group 1 had significantly greater values in the SD score for height ($P < .001$), in the change in the SD score for height ($P < .05$), in the HV (centimeters per year, $P < .05$), and in the change in the SD score for HV ($P < .05$) compared with group 2. The weight of all subjects remained within 1 SD of the mean for HA.

If the individual auxologic effects are adjusted to the different length of therapy, our data indicate that all 10 children in group 1 and 26 of the 31 children in group 2 had an increase in height greater than 0.3 SDs per year and that all 10 children in group 1 and 27 of 31 children in group 2 had an increase in HV greater than 2 SDs per year. Therefore, all children with classic GH deficiency and 27 children (87%) with nonclassic GH deficiency had a satisfactory response to GH therapy.

The predicted adult height was significantly higher ($P < .001$) after the treatment than before: 158.5 ± 5.0 cm vs 152.8 ± 3.4 cm in group 1 and 163.1 ± 4.7 cm vs 157.8 ± 4.0 cm in group 2, with a gain of 5.59 ± 2.94 cm (4.55 ± 1.18 cm per year of therapy) in group 1 and 5.24 ± 2.69 cm (4.53 ± 1.89 cm per year of therapy) in group 2 (P , not significant between the two groups). During the period of treatment, the Δ HA/ Δ BA ra-

tio was 1.28 ± 0.25 in group 1 and 1.39 ± 0.24 in group 2 (P , not significant between the two groups). The only children (in group 2) with a Δ HA/ Δ BA ratio lower than 1 (0.90 during 18 months of therapy) showed an improvement in predicted height of 3.30 cm. Only two children (both in group 2) had an improvement in predicted adult height of less than 2 cm per year of therapy: 1.84 and 1.68 cm/y.

During GH therapy, blood glucose, transaminase, cholesterol, triglyceride, thyroxine, and thyrotropin values remained within the normal range in all children.

COMMENT

Until recently, the limited supplies of pituitary-derived GH have dictated the criteria regulating the administration of the hormone, so that only short children who fulfilled the rigid criteria of classic GH deficiency have been treated. Now we are entering an era in which virtually unlimited supplies of GH are offered to the physician. The logical consequences will be both better management of GH-deficient children and an attempt to promote growth in short children who did not fulfill the above-mentioned criteria. Indeed, some recent studies have clearly demonstrated a good response in HV when short, non-GH-deficient children were given GH.^{10-25,45}

Which short children should receive GH must also be considered from the ethical and economic points of view. The long-term side effects of GH are not known, nor do we know if a short-term increase in growth is a good indicator of a long-term result. These arguments strongly support a careful selection of short children who, though they do not have a GH deficiency by classic criteria, are growing slowly because of possible

Before and After Growth Hormone Therapy*

Δ HA, y	Δ HA/ Δ CA	BA, y	Height Velocity During Growth Hormone Therapy			
			cm/y	SD Score	Δ SD Score	Δ SD Score/y
1.67 \pm 0.71	1.34 \pm 0.16	6.36 \pm 1.45	8.5 \pm 0.9	+2.29 \pm 0.95	+5.56 \pm 0.70	+5.56 \pm 3.14
0.62-2.56	1.16-1.59	4.54-8.39	7.5-10.2	+0.99-+3.62	+4.78-+6.93	+2.45-+11.64
1.63 \pm 0.69	1.33 \pm 0.17	7.46 \pm 1.13	7.7 \pm 0.9	+2.15 \pm 1.16	+4.72 \pm 1.16	+4.91 \pm 2.89
0.54-2.96	1.00-1.76	3.97-9.77	5.8-9.6	-0.36-+4.31	+2.48-+7.28	+1.56-+13.18

treatment. For group 1 vs group 2, $P < .001$ for SD score for height; P was not significant for Δ SD score for height, Δ HA, Δ HA/ Δ CA, SD score for height velocity, and Δ SD score for height velocity per year; and $P < .05$ for Δ SD score for height per year, height velocity, and Δ SD score for height velocity.

decreased GH secretion.

Even if our results do not address the question whether short children with normal, spontaneous GH secretion (mean GH concentration higher than the conventional cutoff of 3 μ g/L) respond to GH therapy, we have demonstrated that the selection of short children based on auxologic features and on the evaluation of spontaneous GH secretion is a reliable method of finding short children who may benefit from GH therapy. Furthermore, this approach is able to select, among the short children who probably would respond to a trial with GH, only those presenting a rationale for GH therapy, ie, a reduced GH secretion and pathologic auxologic features.

Our study has demonstrated that reduced spontaneous 24-hour GH secretion may be detected, in addition to all children with classic GH deficiency (group 1), in short children with pathologic auxologic features, in spite of their normal responses to pharmacologic stimuli (group 2, nonclassic GH deficiency). This condition probably includes the so-called *GH neurosecretory dysfunction*,^{30,46} even if, as suggested by Chalew et al,²¹ this term does not seem to be suitable, because a specific physiopathologic dysregulation in GH secretion has not been demonstrated yet. The normal responses to pharmacologic stimuli in these children might be explained by a subtle abnormality in regulation of GH secretion that may impair only spontaneous GH secretion without altering the responses to conventional provocative testing.

In our children with nonclassic GH deficiency, all spontaneous GH measurements were significantly lower than those of subjects with a mean GH concentration greater than 3 μ g/L

(group 3, short normal children), and all GH values except for mean diurnal GH concentration were significantly higher than those of children with classic GH deficiency. Similarly, Costin and Kauffman³³ and Shulman and Bercu³⁶ have demonstrated intermediate values of spontaneous GH measurements in children with GH neurosecretory dysfunction.

In our study the correlation between mean GH concentration and peak GH concentration after provocative testing was absent for levodopa administration and, as shown by Zadik et al³¹ and Jesuran et al,⁴⁷ modest for insulin tolerance testing. Among the 41 children with a low mean GH concentration, only the 10 with classic GH deficiency (group 1) had low peaks after both pharmacologic stimuli, while the other 31 children with a mean GH concentration lower than 3 μ g/L had either one or two normal GH peaks. Therefore, children with a low spontaneous GH secretion are more numerous than those who may be identified by low responses to provocative testing; Zadik et al³¹ showed that 45% of short children with normal GH peaks in response to pharmacologic stimuli had a spontaneous GH concentration within the range of GH deficiency.

On the other hand, Rose et al³⁸ have recently shown that evaluation of spontaneous GH secretion has less diagnostic accuracy than provocative testing because only 57% of the children given a diagnosis of classic GH deficiency on the basis of pharmacologic stimuli had abnormal responses to the 24-hour spontaneous GH examination. Some of their patients with GH deficiency were growing at 10 cm/y or had a height increase of 1.5 SDs; moreover, some of Rose and colleagues' idiopathic short children had

a very subnormal HV and low somatomedin C values. Nevertheless, falsely low GH responses to provocative testing may occur in normal children and, on the contrary, normal GH values may occur after stimuli in subjects with nonclassic GH deficiency (low spontaneous GH secretion regardless of normal responses to stimuli), some of whom may have mean GH concentrations overlapping those of children with classic GH deficiency.

In our study, mean GH concentration correlated with pretreatment SD score for HV ($P < .001$), SD score for height ($P < .001$), and BA/CA ratio ($P < .02$). Similarly, Albertsson-Wikland and Rosberg³⁷ demonstrated a high correlation between GH secretion and SD score for height, whereas Brook et al,^{8,48} plotting the SD score for HV against the log of the sum of the GH pulse amplitudes, obtained a linear regression. Also, our correlation values of SD score for HV were slightly higher for both the mean pulse amplitude ($r = .604$) and the number of pulses with a GH peak greater than 5 μ g/L ($r = .527$) than for the mean GH concentration ($r = .492$). On the other hand, Costin and Kaufman,³³ Spiliotis et al,³⁰ and Adlar et al⁴⁹ did not find any correlation between mean GH concentration and growth rate or BA.

The correlation between GH secretion and growth has led to the suggestion of treating short children only on the basis of auxologic features regardless of hormonal measurements.^{8,23} However, in our study we have shown that auxologic features alone are not reliable enough to select short children with subnormal mean GH concentrations. Even if children with a mean GH concentration lower than 3 μ g/L (group 2) had, as a group, auxologic features that were statistically different from those of children with a mean GH concentration greater than 3 μ g/L (group 3; $P < .001$ for SD score for height, BA/CA ratio, and SD score for HV), and even if the mean GH concentration correlated with the BA/CA ratio, height, and HV, there was an overlap in auxologic features between the two groups. Indeed, 43 children in group 3 had a mean GH concentration greater than 3 μ g/L in spite of their pathologic auxologic features (BA/CA ratio < 0.8 and SD score for HV more than 1.5 SDs below normal). In any case, a low mean GH con-

centration was not found in any of the 20 short children with nonpathologic auxologic features (short familial stature?).

Short children with a low mean GH concentration (groups 1 and 2) who remained prepubertal throughout the treatment had a good clinical outcome after 6 to 24 months of GH therapy, with an increased linear growth velocity in comparison with the pretreatment value ($P < .001$ for height and HV; $\Delta\text{HA}/\Delta\text{CA}$ ratio > 1) and a better statistical prognosis, demonstrated both by a $\Delta\text{HA}/\Delta\text{BA}$ ratio greater than 1 and by a higher predicted adult height after the treatment ($P < .001$). We found no correlation between mean GH concentration and HV during treatment; Costin and Kaufman³⁸ and Chalew et al²¹ also did not find this correlation. Albertsson-Wikland¹⁸ showed an inverse relationship between response to GH therapy and endogenous GH secretion, and Hindmarsh et al⁶⁰ demonstrated an inverse curvilinear relationship between the pretreatment sum of GH pulse amplitude and the SD score for HV during GH therapy.

There was no significant difference in the change in the SD score for height, ΔHA , $\Delta\text{HA}/\Delta\text{CA}$, the SD score for HV, the change in the SD score for HV per year of therapy, or in the gain of predicted adult height after the therapy between subjects with classic GH deficiency (group 1) and nonclassic GH deficiency (group 2).

Recently, the procollagen III level has been demonstrated to increase parallel to growth during GH therapy.¹⁸ If this is confirmed, the study of procollagen III may provide additional means to predict response to GH therapy.⁵¹

Our study has also demonstrated that several hormonal and auxologic measurements correlated differently with the mean GH concentration. The highest correlations were found with spontaneous GH secretion measurements (mean nocturnal GH concentration, mean diurnal GH concentration, mean pulse amplitude, and number of pulses with a GH peak greater than 5 $\mu\text{g/L}$) and with somatomedin C levels.

The mean nocturnal GH concentration was higher than the mean diurnal GH concentration in the 104 examined subjects both considered as a group ($P < .001$) and in the individual cases. Also, in other studies the nocturnal GH

secretion was higher than the diurnal GH secretion, by evaluation both of the mean GH concentration during 12 or 6 hours and of the only GH peak.^{38,37,38,52,53}

Since a high correlation has been demonstrated between 24-hour and 12-hour spontaneous GH secretion measurements, an interesting issue in the clinical setting is the chance to use the mean nocturnal or diurnal GH concentration as a reliable substitute for the mean GH concentration, halving the duration of the examination. Both Radke et al⁵² and Richards et al⁵³ have shown a significant correlation between mean GH concentration and shorter periods of time. Diurnal GH secretion has not been considered to be as reliable as nocturnal GH secretion in the assessment of spontaneous hormonal secretion, because, as we have shown, diurnal GH secretion is lower than nocturnal GH secretion.^{24,54-56} To confirm the higher reliability of the mean nocturnal GH concentration, we compared the mean GH concentration with both the mean nocturnal and diurnal GH concentration, evaluating the sensitivity and specificity over a 12-hour period on the basis of the cutoff values (3.66 $\mu\text{g/L}$ for nocturnal and 2.33 $\mu\text{g/L}$ for diurnal GH concentration) calculated by the correlation equations that correspond to the conventional value of 3 $\mu\text{g/L}$ for the mean GH concentration. Our data have demonstrated that both the specificity and sensitivity of mean nocturnal GH concentration were higher than those of mean diurnal GH concentration. In any case, it is evident, as Bercu et al³² have pointed out, that the shorter the period of GH evaluation (12 or even 6 hours vs 24 hours), the less sensitive the result, due to the presence of a considerable overlap in GH levels between subjects with levels higher or lower than the cutoff value.

We found a correlation between mean GH concentration and basal somatomedin C levels ($r = .794$). This finding is in agreement with the data of Costin and Kaufman³⁸ in prepubertal children, of Bercu et al,^{32,35} and of Rose et al,³⁸ but not with those of Rochiccioli.⁵⁷ In our study, somatomedin C levels of subjects with nonclassic GH deficiency were higher than those of subjects with classic GH deficiency ($P < .002$) and lower than those of short normal children ($P < .001$). Furthermore, we also found a statistical difference between children

with nonclassic GH deficiency and short normal children ($P < .001$). Nevertheless, the usefulness of evaluation of somatomedin C to separate short children with a low spontaneous secretion of GH from short normal children is limited, because, as for auxologic features, a significant overlap occurs, as others have demonstrated.^{32,38,43,48,58} In fact, 12 (29%) of the 41 children with a mean GH concentration lower than 3 $\mu\text{g/L}$ had a somatomedin C level above 500 IU/L (all in group 2), while in group 3, 12 (19%) of 63 subjects had a somatomedin C value below 500 IU/L. Rochiccioli⁵⁷ showed 26% false-positive and 30% false-negative results in two similar groups. Finally, our study has shown a correlation between somatomedin C concentration and auxologic features (height, HV, BA/CA ratio, and CA), as Cacciari et al,⁵⁸ Costin and Kauffman,³³ and Rayner et al⁶⁰ demonstrated for BA, HV, and CA. On the other hand, Spiliotis et al⁶⁰ did not show a correlation between basal somatomedin C concentration and growth velocity.

In summary, our study has demonstrated that short children with a normal GH response to provocative testing, a mean GH concentration lower than 3 $\mu\text{g/L}$, and pathologic auxologic features (nonclassic GH deficiency) have shown a good outcome in response to GH therapy given for 6 to 24 months. Therefore, we suggest that, in addition to clinical criteria, 24-hour spontaneous GH evaluation is a useful diagnostic procedure in identifying short children who may benefit from GH therapy. Furthermore, 24-hour spontaneous secretion of GH has been shown to be reduced in several but not all short children with pathologic auxologic features, regardless of GH responses to provocative stimuli. Therefore, the occurrence of pathologic auxologic features alone, although very important in considering GH treatment, is not a sufficient criterion to justify treating a short child with GH. The 24-hour GH evaluation also correlated with other spontaneous GH measurements and somatomedin C levels, even if these data alone were not able to indicate which subjects had a low mean GH concentration.

The selection for GH treatment of short children who do not fulfill the rigid criteria of classic GH deficiency must be performed only by experienced pediatric

ric endocrinologists, who are the most qualified physicians to investigate carefully such patients. In any case, further studies on a larger number of children treated for a longer period are necessary to reach definitive conclusions about the efficacy and safety of GH therapy in short children without classic GH deficiency.

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Circumstances Surrounding the Deaths of Children due to Asthma

A Case-Control Study

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• Features of the courses in 12 children who died of an acute attack of asthma were compared with those in 12 children of comparable age and sex who had a life-threatening attack of asthma but survived. Information obtained by structured interviews with the families and physicians and from the medical records was used to characterize (1) the patient, family, severity, and treatment of asthma primarily in the 6 months before the attack and (2) medical circumstances and patient characteristics present on the day of and/or during the acute episode. Patients in the study (mean age, 14.1 years) and controls (mean age, 13.8 years) were in early to late adolescence, had similar long-term medication use histories and an overall rating of the severity of asthma. For the analysis of the information concerning the 6 months before the attacks, the study patients had a greater frequency of respira-

tory failure requiring intubation, a decrease in steroid use in the month before the attack, history of family disturbance, abnormal reaction to separation or loss, and expressed hopelessness and despair. For the period more immediately surrounding the acute attack, study patients more often had attacks starting during sleep, but less frequently experienced vomiting during the course of the attacks. Treatment of the attack by the parents was poor (primarily because of delays) in 7 of the 12 children who died, but was also a factor in 6 of the 12 controls. Our data suggest that certain characteristics of asthmatic children may place them at greater risk for death due to their asthma. In addition, we postulate that there may be inherent differences in the mechanisms of the acute attacks between the children who died and those who survived.

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Death due to asthma can occur suddenly^{1,2} or after a prolonged attack that has not been treated optimally.^{3,4} Since the 1960s most deaths have occurred outside of hospitals,^{2,3,6,8} although some continue to occur during hospitalization for asthma.^{7,8} Thorough reviews of cases in the United Kingdom and New Zealand have identified potentially avoidable factors contributing to deaths in a large percentage of cases.

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This was true both for deaths outside of the hospital^{3,9} and in the hospital.⁸ Issues most often cited were poor utilization of corticosteroids and bronchodilator drugs, poor cooperation of the patient with the management of the asthma, failure to recognize the severity of the attack by patients, relatives, and physicians associated with delays in starting appropriate treatment, and inadequate responses of medical services to emergency calls.^{6,9,10}

Circumstances surrounding the deaths due to asthma were first investigated by Fraser et al,¹¹ who focused on bronchodilator and corticosteroid therapy. Excessive inhalation of bronchodilators was thought to have contributed to death in 37% of the patients, primarily by delaying medical advice. In 1984, Johnson et al⁸ found four sets of circumstances in the fatal attack contributing

to deaths: patient failure to recognize severity of the attack, rapid progression in attack severity, misjudgment in management, and delay from many causes. In 1987, Rea et al¹⁰ found many of these same factors. They also noted that some of those who died were unusually fearful or anxious, and some had premonitions of death 1 or 2 days before the event. Finally, the British Thoracic Society¹² has concluded that allergy may play a role in the deaths of some patients. None of the studies concerning the circumstances surrounding death due to asthma was case controlled.

The purpose of our study was to compare the life circumstances and course of events in children who died of an acute asthma episode with those in children who suffered a life-threatening attack of asthma but survived.

PATIENTS AND METHODS

Patients

All subjects were known to have asthma as defined by the American Thoracic Society.¹³ Subjects were identified by physicians primarily in response to a letter sent by the investigators to all former fellows of both the Departments of Pediatrics and Internal Medicine at the National Jewish Center for Immunology and Respiratory Medicine, Denver, Colo. In some cases, the investigators were contacted spontaneously because of their known interest in the problem of asthma mortality.

The cases of 12 children who had died during an acute attack of asthma were referred and utilized for the study. All were judged to have died of acute asthma by both their physicians and the local coroner. One patient died during a hospitalization for increasing asthma, and the rest died at home before resuscitation could be started, during resuscitation at home, or en route to an hospital emergency department. Controls had sur-

vived a "life-threatening" episode of asthma, defined as asthma complicated by respiratory failure, requiring either intubation and ventilation (8 patients) or intravenous isoproterenol (4 patients). When there had been more than one episode of respiratory failure, the most recent was used as the index episode for the study. We selected subjects who had had the index episode within 3 years of the study to assure good recall of the events by parents. The study and control groups were comparable for age and sex.

The study design was approved by the Institutional Review Board at the National Jewish Center for Immunology and Respiratory Medicine. Parents gave verbal consent for their participation in the study. Written consent was obtained to request medical records from their physicians and the hospital(s) involved in the treatment of the index asthma attack.

Interviews of Families and Physicians and Compilation of the Data

Variables for analysis were obtained from three sources: (1) review of literature on asthma mortality that focused on factors important in outcome of severe asthma attacks,^{3,5-7,9,11,12,14} (2) two previous case-control studies on risk factors for asthma mortality,^{15,16} and (3) the investigators' experience in dealing with patients who have died or have had a near death experience from asthma.

The data for this study were obtained by interviews of families and physicians who had cared for the children, from hospital/emergency department records pertaining to the index episode, and from the physician's office records for the 6 months before the episode. The families were each interviewed for 1 to 2 hours, using a semistructured interview, by one of us (B.D.M.). The information was checked for consistency by determining the answer using several different approaches at varied times in the interview. In each case the person responsible for the care of the child at the time of the index episode was interviewed. If this person was different from the usual primary care giver, both individuals were interviewed. These interviews were tape recorded for subsequent reference and further analysis.

The physicians were contacted and interviewed, using a structured interview, by one of us (R.C.S.). Each physician was asked exactly the same set of questions. If the primary physician had not been involved in the acute episode, more than one physician was interviewed to gain a complete database for the patient. Areas covered in the physician interview were similar to those covered in the interview of the parents, except that relatively more emphasis was placed on obtain-

ing information characterizing the patient's asthma, the physician's care—both long-term and in the days preceding the episode—and the events and treatment during the index episode. Hospital/emergency department records and records from the physician's office were examined in most cases to confirm information obtained during the physician interviews.

Immediately after completion of the interviews, each investigator scored each of the variables. A composite summary was then developed by both investigators. The rating was obtained primarily from a single source for some of the variables (indicated below) or from consideration of all three sources. When the rating for an item was different between the sources, the tape of the parent interview,

the written record of the structured physician interview, and the medical records were reviewed again and a judgment was made by consensus of both investigators as to the most accurate data source. If sufficient information was not obtained to score an item, the item was removed from the analysis for the patient.

Asthma, Treatment, and Capabilities of the Child and Family

The variables that were analyzed are summarized in Table 1. The period 6 months before the episode was emphasized. Six variables were used to assess the physiologic status of the patient before the index episode. Asthma severity was assessed by parent and physician interviews and office

Table 1.—Information Characterizing the Patient, Family and Severity and Treatment of the Asthma Before the Attack

Variable	No. of Patients With Variable		P*
	Study Patients	Control Patients	
Physiologic			
Severe asthma	8	5	NS
History of respiratory failure requiring ventilation†	10	3	.006
Decrease in steroid dosage >50% in month before attack†	6	1	.034
Use of inhaled steroids†	5	8	NS
Fatigue	6	10	NS
Unstable asthma for more than 3 days before final attack	4	6	NS
Psychologic			
Family dysfunction†	7	2	.045
Reaction to separation or loss†	10	2	.002
Wheezing with stress†	6	5	NS
Disregard of perceived asthma symptoms†	8	8	NS
Patient-parent conflict†	4	3	NS
Patient-physician conflict†	3	1	NS
Parent-physician conflict†	1	0	NS
Manipulative use of asthma†	0	1	NS
Emotional disturbance†	1	1	NS
Depression†	2	3	NS
Life stressors	4.6	2.7	NS
Hopelessness/despair within 1 month before attack	8	3	.05
Quality of asthma care			
Poor self-care†	7	8	NS
Patient-parent factors adversely affecting care	4	5	NS
Physician factors adversely affecting care	5	3	NS

*P>.10 for values that were not significant (NS).

†These variables were analyzed with a one-tailed test (all others were analyzed with a two-tailed test). These 14 variables have been described previously as distinguishing between children who died of asthma from patients matched for age and overall severity of asthma but known to be alive.¹⁵ They were modified slightly from the previous descriptions to emphasize observations made by the parents and physicians in the 6 months before the index episode (see "Patients and Methods" section). The remaining variables are defined in the "Patients and Methods" section.

records, which included presence of significant asthma symptoms at least once a week for the previous year (primarily from parent report), more than two hospitalizations for asthma in the previous year, more than four emergency department visits in the previous year (parent and physician reports and records), use of oral corticosteroids at least every other day throughout the previous year (primarily from office records), history of rapidly progressing attacks (parent and physician reports), and episodes of loss of consciousness with asthma attacks (parent and physician reports). Presence of three or more of the six criteria defined severe asthma.

History of respiratory failure requiring ventilation was obtained primarily from the physician (no patient had a history of hypoxic seizures with acute asthma attacks). Steroid reduction was defined as a decrease in oral steroid doses by more than 50% within the month before the index episode (office records). Administration of inhaled steroids occurred in the month before the episode (office records). Fatigue or exhaustion were rated when the parents stated that the child had been excessively fatigued within 2 days before the attack. Unstable asthma for more than 3 days before the attack was rated by evidence for increased asthma symptoms in the week before the attack; the information was gained either from the physician record or parent observation of the child's course (the parents frequently had been aware of instability but had not contacted the physician). The precipitating factors for the asthma had not been uniformly evaluated by the physicians; thus, the basis for the severity of the asthma was not evaluated.

Twelve variables assessed the psychologic status of the index and control subjects; ratings were made on the basis of historical report from the parent, care giver, and treating physician. Ratings were made by one of us (B.D.M.) based on the following guidelines. Family dysfunction was rated on the basis of a number of issues, such as the presence of marital discord, lack of emotional support of the child by one or more parent/care giver, presence of parental drug or alcohol abuse, financial instability, lack of consistent support for medical treatment, and lack of extrafamilial psychosocial support systems. Reaction to separation or loss was rated if the child frequently had developmentally inappropriate responses to brief separations from a parent or caregiver (eg, problems with going to school, staying with a babysitter, or enduring other brief parental absences), or if the child had suffered a significant loss within the 6 months before the attack (eg, death of a parent or sibling, loss through divorce or desertion).

Wheezing with stress was rated when the parents and physician considered emotional

stress a frequent precipitating factor for acute asthma episodes and reported that as a problem. Disregard of perceived asthma symptoms were scored if the patient reportedly took no action in response to recognized asthma symptoms. Examples of such behavior included not stopping exercise after clear wheezing had started or failing to self-medicate according to protocol when symptoms warranted. At least two clear instances of such behavior in the 6 months before the event noted by either parent or physician constituted a positive score. Patient-parent conflict, patient-physician conflict, and parent-physician conflict were rated as positive if conflict was reported and corroborated either by the parents and/or physician in any of the three categories; conflict was defined as an ongoing problematic relationship engendering emotional discord consisting of disagreement, frustration, and dissatisfaction. This conflict had to be ongoing throughout the 6 months preceding the index episode. Manipulative use of asthma was rated if the child reportedly used asthma symptoms for secondary gain, eg, to avoid unpleasant tasks, to place pressure on others to respond to the child's wishes, or to seek attention; problems reported in this domain and at least two specific instances of such behavior in the 6 months preceding the index episode constituted a positive score.

Emotional disturbance was rated if the child had been referred for psychiatric treatment within the 6-month period before the event, or if the child appeared to have been experiencing problematic functioning, using guidelines set forth in the Child Global Assessment Scale.¹⁷ Depression was rated on the basis of reported clinical symptoms using the Children's Depression Rating Scale-Revised¹⁸ as a guideline for assessment, or if the child had been treated for depression within 6 months of the index episode.

Life stressors assessed the presence of stressful situations within 6 months of the events that were thought to have affected asthma symptoms or general functioning. There were 10 specific areas of exploration: geographic relocation, recent loss of a family member, parental separation or divorce, school problems, alcohol or other drug abuse, major social upheaval, involvement with the law, short-term illness/hospitalization of family member, attempted suicide of a friend or family member, or two or more hospitalizations of the child. A score of 0 to 10 was recorded for each patient. The emotional state of hopelessness/despair was scored positive if the child was reported to have expressed feelings of hopelessness, a wish to die, or direct or indirect references to suicide or (patient's own) death within 1 month before the index episode.

Quality of asthma care was assessed by

three variables. Poor self-care was rated when the parents and/or physician stated that there were regular problems with the child's ability to respond in an age-appropriate manner to asthma symptoms and to attend to routine, prophylactic care. Patient-parent factors affecting care adversely were assessed with six factors: a consistent care provider (parent and physician reports), calling the physician within 8 hours after the onset of wheezing "most of the time" (physician), taking the child to the physician within 24 hours after the onset of wheezing if there was no response to the usual treatment "most of the time" (physician), keeping scheduled office visits or calling to reschedule for conflicts (physician), correct use of metered-dose inhalers (parent and physician), and parent admission of noncompliance by the child. Patient-parent factors were judged to be present if two or more of these factors were reported to be deficient.

Physician factors adversely affecting care was assessed by seven factors, all of which were judged during the physician interview or by examining office records. The variables included providing specific instructions to the parents concerning when to call and when to arrange a visit during wheezing episodes, arranging follow-up within 48 hours after hospitalization (either an office visit or telephone call), arranging follow-up within 24 hours after an emergency department visit, scheduling office visits every other month during the 6 months before the episode, conducting spirometry measurements at the time of office visits, arranging follow-up within 2 weeks of reduction of steroid dosage by greater than 50%, and measuring theophylline levels at least once within the 6 months before the episode if doses greater than 20 mg/kg were prescribed. Physician factors were judged to be present if problems occurred in two or more of these areas.

Medical Circumstances and Patient Characteristics Present on the Day of and/or During the Acute Episode

These variables are summarized in Table 2. For the variable attack that began during sleep, the time of day and whether the attack occurred as the patient awoke from sleep (either during the night or with a nap during the day) were assessed by parent history. The rate of progression of the attack was assessed by asking the parents and the physician how fast the patient progressed from the state of health present in the last week until resuscitation or emergency department treatment was started; progression in less than 1 hour was considered rapid.

Treatment of the attack was assessed using four variables: whether immediate treatment was begun once the change in course

Table 2.—Medical Circumstances and Patient Characteristics Present on the Day of and/or During the Acute Asthma Attack

Variable	No. of Patients With Variable		P*
	Study Patients	Control Patients	
Attack began during sleep†	7	2	.045
Rapid progression of attack	9	5	NS
Poor treatment of attack (delays)	7	6	NS
Inadequate steroid use	4	4	NS
Inadequate assessment			
By patient or parent	6	6	NS
By physician	1	0	NS
Vomiting	1‡	8	.01
Response time, min	10	15	NS
Poor emergency care during final attack	3	0	NS

* $P > .10$ for values that were not significant (NS).

†Attack began during the night did not distinguish study patients from controls ($n = 7$ in study patients; $n = 4$ in controls; $P = .30$).

‡This patient vomited and then aspirated the vomitus.

was noted, whether this treatment was appropriate (eg, use of inhaled β_2 -agonists), whether there was a delay in calling for help (a call to physician or emergency squad should have been made as soon as a change in course was apparent), and whether there was an overuse of β_2 -agonists (more than 12 nebulizer treatments in the final 24 hours). In most cases, the physician had not been involved in the care within the last 24 hours. Therefore, parent report was used primarily. Initial history in emergency department records were used when complete. Poor treatment was scored if two or more of these variables were present.

Inadequate use of steroids in the final course was scored if there was sufficient cause for their use in time for them to be started, but they were not started or increased from their usual long-term dosage. Sufficient cause for using steroids included scenarios such as being seen in the emergency department within 1 week of the episode with increased asthma that did not respond to the treatment prescribed, having increased asthma symptoms during a hospitalization, having increasingly more severe asthma for at least 24 hours, and using increasingly more β_2 -agonist by inhalation for at least 24 hours without affecting the course.

Inadequate assessment of the severity of the attack by the patient or parent was scored when there appeared to the investigators that there was adequate reason for concern about the progress of the asthma symptoms but no call was made to the physician. Inadequate assessment by the physician was scored when the severity of the attack was not understood and adequate care was not administered (eg, the physician was aware of

frequent use of inhaled β_2 -agonists, but did not initiate steroid therapy when response to bronchodilators was inadequate). Vomiting was scored when it occurred during the period of rapid progression of symptoms before the final loss of consciousness or intubation attempt(s).

Response time in minutes was considered from the call to the emergency department by the parents, or getting into the car to travel to the emergency department, until the initiation of care. Poor emergency care during the final episode was scored when emergency squads did not have epinephrine or oxygen available, or when extreme disorganization of the resuscitation attempt interfered with intubation and/or administration of intravenous fluids.

Analysis of Data

Each variable or variable grouping was studied independently to determine possible differences between the study patients and controls; 2×2 contingency table analysis (Fisher's Exact Test) was used for present/absent data, and Wilcoxon's two-sample test was used for noninterval data. When the direction of a result had been described in previous studies, a one-tailed test was used. All other results were examined using a two-tailed test.

RESULTS

Asthma, Treatment, and Capabilities of the Child and Family

Study patients and controls were in early to late adolescence. Patients studied included 8 boys and 4 girls with a mean age of 14.1 years (range, 10 to 18

years); control patients included 9 boys and 3 girls with a mean age of 13.8 years (range, 11 to 17 years). Most of the episodes occurred during the months of May through June or September through October (9 in the study group and 8 in the control group).

Overall severity of asthma was similar in the two groups. The medications used for a long period were similar in the two groups. All patients in both groups had used oral steroids at some time. Five in the study patients and six controls had used oral steroids at least every other day in the year before the attack. Nine of the study patients and 11 of the controls used theophylline (anhydrous), 11 in each group used inhaled β -adrenergic agents by air compressor, and 7 in the study group and 11 of the controls used inhaled β -adrenergic agents by a metered-dose inhaler. The total amount of medication required for control of asthma was also similar in the two groups: number of medications for study patients was a median of 6 with a range of 1 to 10 compared with 5 (range, 3 to 6) for the controls; total number of doses of asthma medications in a 24-hour period for study patients was a median of 11 with a range of 1 to 21 compared with 11 (range, 6 to 15) for the controls.

Two physiologic variables listed in Table 1 distinguished between the two groups: history of respiratory failure requiring intubation and reduction of steroids by more than 50% in the month before the event. The remaining physiologic variables—use of inhaled steroids, fatigue, and unstable asthma in the week before the final attack—were present in approximately 50% of each group and did not distinguish between the two groups.

Three psychological variables distinguished between the two groups (Table 1): presence of family dysfunction, history of reactions to separation or loss, and hopelessness/despair in the month before the attack. The remaining variables did not distinguish between the groups. Two variables were present in many of both study patients and controls: wheezing with stress and disregard of perceived asthma symptoms. Seven variables were present in a minority of both study patients and controls: patient-parent conflict, patient-

physician conflict, parent-physician conflict, manipulative use of asthma, emotional disturbance, depression, and life stressors. None of the variables reflecting the quality of care of the asthma distinguished between groups.

Medical Circumstances and Patient Characteristics Present on the Day of and/or During the Acute Episode

Two variables distinguished the study cases from the controls: attacks beginning during sleep and vomiting during the attack. Rapid progression of the attack, inadequate assessment by patient or parent, and poor treatment of the attack were prominent in both study patients and controls and did not distinguish one group from the other. While rapid progression of the attack (within 1 hour) did not distinguish study patients from controls, four of the study patients had such rapid progression that the child was moribund by the time resuscitative efforts were initiated. In these four patients there had been no delay in the parent seeking help or in arrival of the emergency squad. Poor treatment was scored in seven study patients and six controls (Table 1), at least in part because there had been delays in calling for help. Inadequate steroid use, inadequate assessment by the physician, or poor quality of care during the final episode were not frequently present in either group.

COMMENT

The results of our study identified differences between children who died during an acute attack of asthma and those who suffered a life-threatening attack but survived. Asthmatics who died had severe disease (history of respiratory failure), periods of medical instability (reductions in steroid therapy), and significant psychosocial problems (increased sensitivity or extreme reactions to separation or loss, a history of family turmoil, and expressed hopelessness or despair). These findings may have been associated with death due to asthma because of the inability of the patients and/or families to react appropriately to rapid changes in the course of severe asthma. Failure to assess the severity of the asthma in an objective fashion and other components of physician care are mentioned frequently as

factors associated with asthma deaths, but were not different between our study and control groups.

Increased sensitivity or extreme reactions to separation or loss and a history of family turmoil have been identified in a number of other studies,^{9,16,19-21} where they were considered traits characterizing the patient/family during some (often unspecified) period preceding the asthma death. However, these psychosocial areas had not been identified previously as active problems in the months immediately preceding death. Emotional disturbance and depression have also been noted as features characteristic of patients who have died of asthma,^{15,16,19,22-25} but neither variable was discriminating in our study. Our results may be related to the relatively stricter definitions used for these conditions compared with those in previous studies; we used psychometric scales and/or an outside professional diagnosis to make a positive rating, and the condition had to be active during the 6 months before death. Hopelessness/despair did discriminate between our two groups. This emotional state is a frequent finding in patients with depression or other forms of emotional disturbance, although hopelessness/despair alone is not sufficient to make a diagnosis of depression. Hopelessness is a discrete emotional state that can be identified at least transiently in many patients suffering from chronic illness, in persons who have suffered a severe physical insult, or in persons who have experienced an important loss.

For the period in and around the time of the acute attacks, nine variables were considered, but only attacks beginning during sleep and vomiting during the attack showed a statistical difference between the two groups (Table 2). Attacks occurring during sleep were considered separately from attacks at night because the physiologic definition of sleep is different from the circadian rhythm of day-night cycles. One such difference is the relative shift to a cholinergic predominance in the central and peripheral nervous systems that occurs during sleep.²⁶ This shift is independent of the circadian rhythm of night and day cycles. Such a neural shift during sleep could increase reactivity of the airways to an asthma trigger. These neurally

mediated changes could explain the suddenness and irreversibility of attacks that begin during sleep. The four study children who experienced sudden collapse after arousal from sleep died as they were attempting to administer some self-treatment for asthma or before help could be summoned. The emotional state of hopelessness/despair is also known to be associated with central and peripheral disturbances in the autonomic nervous system indicative of a relative cholinergic dominance²⁷⁻³¹ and could synergize with the physiologic changes occurring during sleep, with both contributing to a rapid progression and irreversibility of symptoms.³²⁻³⁴

Patients who survived their severe attack were more likely to have vomited during the attack. Before the index attacks, patients in both groups had had vomiting with severe asthma. Vomiting with the previous attacks was almost always described as "bringing about relief of symptoms of asthma almost immediately." The reason(s) that vomiting did not occur during the episodes that preceded the deaths is not known. Although the clinical phenomenon of vomiting producing relief of an asthma attack is well documented,²² no empirical studies have confirmed a mechanism; the flushing, sweating, tachycardia, and tachypnea that follow extreme retching and vomiting suggest that neural pathways may be involved. Vomiting was not always beneficial, however. In one study case of a 10-year-old boy, vomiting occurred after the child had become semiconscious and was receiving cardiopulmonary resuscitation. He aspirated vomitus and apparently suffocated as a result. This child was reported to have vomited during his only other severe asthma episode with consequent immediate relief of symptoms.

Controls were selected for severity of the single asthma episode. They also had an overall severity that was similar to the children who died, as indicated by the overall severity score (Table 1) and the similarities between medication use in the two groups. It is possible that the two groups might have been distinguished from each other if additional studies, such as methacholine reactivity, could have been done. It is also possible that individuals in the two groups

may have had different sensitivities to adverse side effects of the medications used; however, there is no indication that types of medications or the complexity of the medical regimens contributed to the deaths. Neither quality of care given by the parents or the physicians nor the presence of life stressors distinguished between the groups (Table 1). Index episodes occurred most frequently during either spring or fall months in both groups. These periods coincide with periods of the highest prevalence of airborne allergens and may reflect a role for allergy in the episodes for both groups of children.

The need for adequate emergency treatment early in the course of an acute asthma attack is clear. Problems with delays were apparent in many of the study patients, but also in many of the controls. Poor care by the responding paramedic units occurred only in study patients for whom there had been delays in calling the squad. The quality of care may have been affected by the catastrophic nature of the situation at the time of arrival of the squad. While rapid and precise care of emergent asthma by paramedic squads is essential, the apparent misjudgment of the parents in delaying the call for help remains a primary concern.

In summary, the children who died of asthma and were studied in this report differed in the 6 months before their deaths than children who had a severe attack of asthma but survived. However, the circumstances immediately before and during a fatal episode may be the most important issues. Neural instability may be important in producing differences in the course of a severe attack that can lead to a fatality. The role of the factors apparent in the 6 months preceding the attacks in producing the rapid onset and often irreversible bron-

chospasm is unclear and requires further investigation.

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In Other AMA Journals

JAMA

Management of Infectious Waste by US Hospitals

W. A. Rutala; R. L. Odette; G. P. Samsa (JAMA. 1989;262:1635)

Clinical Trial of Single-Dose Intravenous Gamma Globulin in Acute Kawasaki Disease

Preliminary Report

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• Gamma globulin administered in a single dose of 1 g/kg of body weight intravenously caused prompt clinical improvement in 27 of 32 consecutive children with Kawasaki disease treated by the 12th day of illness. Response was equally good for the 20 children treated in the first week and the 12 treated in the second week. Fever and clinical signs abated within the first day after treatment, the mean white blood cell count normalized by 48 hours, and the sedimentation rate continued to be elevated for about 2 weeks, while the platelet count rose during the first 2 weeks after treatment and returned to normal approximately 1 month after treatment. Five children with incomplete relief needed more than the single dose before resolution of signs and symptoms occurred. Coronary aneurysms in 2 patients before treatment regressed by 2 weeks. No patient developed coronary aneurysms. No child had sequelae of Kawasaki disease at a follow-up of 2 to 31 months. We believe that although this was a one-arm, uncontrolled pilot study, the results suggest that this protocol provides a safe, flexible, and effective treatment for acute Kawasaki disease.

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Kawasaki disease (KD) is complicated by a 20% to 25% incidence of coronary aneurysms when children are

treated with aspirin alone.^{1,4} A multicenter, randomized, controlled trial of intravenous gamma globulin (400 mg/kg of body weight for 4 days) with aspirin vs aspirin alone demonstrated in August 1986 an unequivocal reduction in incidence of coronary artery abnormalities as well as prompt resolution of clinical and laboratory abnormalities in KD in the group treated with gamma globulin and aspirin.⁵ Others reported similarly encouraging results.^{6,7} We postulated that a large dose of gamma globulin in 1 day of treatment might be as effective in preventing coronary abnormalities and in terminating clinical illness. If so, such a regimen could provide an economic as well as a health benefit. Therefore, in November 1986, we began a pilot study in consecutive children in the acute febrile stage of KD to administer gamma globulin in a single dose of 1 gm/kg, which could be repeated in 48 to 72 hours if needed for relief of symptoms and signs.

PATIENTS AND METHODS

The treatment protocol in our feasibility study used a single dose of 1 g/kg^{8,9} of gamma globulin plus 100 mg/kg of aspirin until the patients were afebrile for 1 day. Each child who met the criteria for diagnosis¹⁰ and who came to us within 14 days of the onset of illness entered the study. The first day of fever was taken to be the first day of disease. Our pilot study was conducted as an open-label, uncontrolled, one-arm clinical trial as opposed to a controlled, randomized trial for two reasons. First, we wanted to determine the safety and efficacy of this dosage as quickly as possible. Second, a controlled, randomized trial would have required several hundred patients to demonstrate a 75% decrease in the failure rate at 2 weeks found in the controlled study⁵ of 8% down to 2%. That was not possible.

We chose 1 g/kg rather than a lower or higher dose because it was the largest dose in 1 day for which considerable experience had been accumulated that demonstrated safety.^{8,9} We were concerned that a higher dose than this might overload the circulatory system in these patients with myocarditis.

Because our experience with 110 children with KD between 1980 and 1986 had demonstrated no difference in the incidence of coronary abnormalities between those patients receiving high-, medium-, or low-dose aspirin⁴, we limited the use of high-dose aspirin to the period of fever plus 24 hours. We then reduced it to a low, platelet-inhibiting dose for 2 months.

The Institutional Committee on Human Rights in Research gave permission to undertake this study. All parents signed informed consent for their children.

Patient Assessment and Laboratory Evaluation

On patient admission, we confirmed the diagnosis of KD¹⁰ and obtained electrocardiograms, M-mode and two-dimensional Doppler echocardiograms, chest roentgenograms, complete blood cell counts with platelet count and erythrocyte sedimentation rate, blood chemistry values, and urinalysis results. We repeated the blood studies, electrocardiograms, and echocardiograms once or twice weekly in the first 2 weeks after treatment, at 1 and 2 months, 6 and 12 months, and 2 years after onset. If coronary involvement has not been demonstrated by 2 months, it is highly unlikely that aneurysms will develop thereafter.

Two experienced echocardiographers, nonblinded collaborating investigators, interpreted and agreed on findings of the echocardiograms, using generally accepted criteria,¹¹⁻¹⁸ as in previous reports from our laboratory for studies on KD^{4,14} and as in the Newburger et al⁵ controlled study. Evidence of pericardial effusion, myocardial dysfunction, and valvular regurgitation was sought. With the use of two-dimensional echocar-

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diography, we evaluated the proximal portions of the left main coronary, left anterior descending, and circumflex coronary arteries, and we viewed the origin of the right coronary artery and its course in the atrioventricular groove. The presence of dilatation or aneurysm was interpreted as an abnormality.

Intravenous Gamma Globulin Treatment

The patients received intravenous gamma globulin as a lyophilized product reconstituted to a 5% to 6% solution and given over a 6- to 8-hour period. The gamma globulin preparations were those in regular use in our hospital: Gammagard (Hyland Therapeutics Division, Travenol Laboratories Inc, Glendale, Calif) and Sandoglobulin (Swiss Red Cross, Berne, Switzerland; Sandoz Pharmaceuticals Corp, East Hanover, NJ, distributor).^{15,16}

Aspirin

We gave 100 mg/kg of aspirin daily in four doses until fever had abated for 24 hours. Then we reduced the aspirin to one fourth to one whole baby aspirin (82 mg) daily for 2 months for its effect on inhibiting platelet aggregation.

Methods

Fisher's Exact Test was used to compare the rates of coronary abnormalities at 2 weeks and 2 months in our study with that of Newburger et al.⁵ Among the three treatment groups, when a significant difference ($P < .05$) was found, pairwise comparisons of each group were made using Fisher's Exact Test with a Bonferroni adjustment to account for multiple comparisons.

RESULTS

Patient Characteristics

From November 1986 through March 1989, we treated 32 consecutive patients with typical KD,¹⁰ 20 by the seventh day and 12 between the eighth and 12th days. Twenty-three children had the onset of illness in the 5 months between April and August. Ages ranged from 8 months to 13 years (mean, 3.5 years), and 7 were less than 1 year of age. Eighteen were male. Racial or ethnic distribution included 11 black, 9 white, 8 Asian, and 4 Hispanic children.

Clinical Features

In addition to the usual signs (sustained fever, rash, changes in mucous membranes and tongue, edema and erythema of hands and feet, cervical ad-

enopathy, conjunctivitis, and irritability), seven patients each had arthralgia and diarrhea, three complained of abdominal pain, one had hepatitis and hydrops of the gallbladder, and one had orchitis.

Risk Factors for Coronary Artery Involvement

Using the risk factors that were statistically significant in our previous report on 25 patients with coronary artery disease among 110 consecutive patients with KD treated by us with aspirin alone between January 1980 and August 1986,⁴ we found one or more risk factors in all but 1 patient. Since all children were treated by day 12 of illness, the single most significant risk factor (fever for 2 weeks or more) did not apply. Fourteen children had an erythrocyte sedimentation rate that exceeded 100 mm/h, 10 of them before they were given intravenous gamma globulin, but only 6 had such a high erythrocyte sedimentation rate in the first week. Thirteen patients had pericardial effusion, evident in each on admission. Eleven had a platelet count greater than $1 \times 10^{12}/L$ but only 2 children, both treated on day 12, had such a high count before administration of intravenous gamma globulin.

Response of Clinical Features

Twenty-seven children experienced prompt and dramatic clinical improvement that continued through discharge and follow-up. The mean highest temperature within the 24 hours before intravenous gamma globulin administration was $39.4^{\circ}C$ and $37.5^{\circ}C$ within 24 hours after the dose was administered. Fever did not return. There was no difference in response between the 18 children treated in the first week ($39.5^{\circ}C$ down to $37.6^{\circ}C$) and the 9 treated in the second week ($39.2^{\circ}C$ down to $37.4^{\circ}C$). They received the single dose of intravenous gamma globulin.

Five children received a dose of more than 1 g/kg of intravenous gamma globulin. One, a 2½-year-old boy, was transferred to us after failure to respond to two doses of 400 mg/kg of intravenous gamma globulin on the ninth and 10th days of illness. Clinical features cleared after 24 to 48 hours of 1 dose of 1 g/kg of intravenous gamma globulin. A second

child, aged 4½ years, failed to show improvement after a 4-day course of 400 mg/kg of intravenous gamma globulin on the fifth through ninth days of illness. On admission to The New York Hospital, New York, NY, on day 10, her temperature was $39.4^{\circ}C$, and she fulfilled all criteria for KD. She received 1 g/kg of intravenous gamma globulin on day 11 and showed improvement but remained febrile, with a temperature of $38.6^{\circ}C$. Therefore, she received a second dose of 1 g/kg. Signs and symptoms completely abated. Three other children, one with a coronary aneurysm before intravenous gamma globulin administration, had incomplete relief after the single dose and received a second dose 48 to 72 hours later, followed by further improvement. In these children, the mean high temperatures before and after the first dose were $39.3^{\circ}C$ and $38.4^{\circ}C$, respectively. After the second dose, it was $37.3^{\circ}C$. Two of the five patients who received more than the single dose of intravenous gamma globulin were treated in the first week.

Response of Laboratory Findings

Within 48 hours of administration of the intravenous gamma globulin, the elevated white blood cell count with leftward shift decreased in all but those who were re-treated. Before administration of intravenous gamma globulin, the mean white blood cell count was $18.6 \times 10^9/L$, and 2 days later it was $11.5 \times 10^9/L$. There was no significant difference between those patients treated in the first week ($18.8 \times 10^9/L$ down to $11.5 \times 10^9/L$) and those treated in the second week ($18.5 \times 10^9/L$ down to $7.2 \times 10^9/L$).

Before treatment with intravenous gamma globulin, the mean erythrocyte sedimentation rate was 73.7 mm/h. After 48 hours and at 1 week, the mean erythrocyte sedimentation rate remained elevated (79.4 mm/h and 73.3 mm/h, respectively) before it declined to a mean value of 48.8 mm/h at 2 weeks and 29.8 mm/h at 1 month. The erythrocyte sedimentation rate exceeded 100 mm/h in 14 children. Ten of them, including 3 children who received two doses of intravenous gamma globulin and 6 children treated in the first week, had an erythrocyte sedimentation rate of greater than 100 mm/h before admin-

istration of intravenous gamma globulin.

The mean platelet count was slightly elevated before administration of intravenous gamma globulin to $535 \times 10^9/L$. Children treated in the first week had a lower mean platelet count ($414.4 \times 10^9/L$) than did those treated in the second week ($701.7 \times 10^9/L$) ($P < .001$). The count was higher than normal in only 9 of 20 children treated in the first week, yet it was higher than normal in 11 of 12 children treated in the second week ($P < .001$). Thrombocytosis greater than $1 \times 10^9/L$ occurred before administration of intravenous gamma globulin in only 2 children, both in their 12th day of sickness, and after administration of intravenous gamma globulin in 9 more. In general, the count rose through the second and third weeks and normalized by 1 month after treatment.

Thirteen children had abnormal electrocardiograms on admission with changes in ST segments and T waves (12 children) and with prolonged PR interval (1 child). Tracings were normal by 1 week, but during convalescence the T waves in leads V5 and V6 became tall and peaked¹⁵ in 18 patients, 9 of whom had had a normal electrocardiogram before treatment.

Effect on Coronary Arteries

No child developed abnormalities of the coronary arteries after the intravenous gamma globulin treatment was begun. The follow-up has been from 2 to 31 months, with 15 patients under observation for longer than 1 year. Before treatment on the sixth day of illness, 2 boys had coronary aneurysms, 1 involving the right coronary artery and the other at the origin of the left main coronary artery and at the bifurcation with the left anterior descending artery. Because of persistence of fever, leukocytosis, and symptoms, the first child received a second infusion of 1 g/kg of intravenous gamma globulin 48 hours after the first. In both instances, aneurysms resolved by 2 weeks.

Pericardial Effusions.—Pericardial effusions present in 13 patients at admission (12 in the first week), disappeared by the second week after therapy. No patient developed an effusion after treatment.

Myocardial Abnormality.—In only

one child (treated on day 5) was the ejection fraction before administration of intravenous gamma globulin low (54%) and the left ventricular dimension above normal. On the next day the ejection fraction was 60% and the left ventricle was less enlarged. No patient developed echocardiographic changes of myocardial impairment during the follow-up.

Valvular Regurgitation.—Valvular regurgitation was not found by auscultation or Doppler echocardiography before or after intravenous gamma globulin.

Days of Hospitalization.—The mean New York Hospital stay was 4.4 days, and the median was 4 days. One child was treated as an ambulatory patient. No short-term unfavorable reaction took place in any patient during or soon after infusion of gamma globulin. A 9-year-old boy developed a transient, passive, Coomb's-positive hemolysis caused by an anti-B alloantibody.

Aspirin Therapy.—Because most children were treated with intravenous gamma globulin on the day of admission and were afebrile in 24 hours, only five children received full-dose aspirin therapy for longer than 2 or 3 days.

COMMENT

The primary goal of this clinical trial with a new regimen for intravenous gamma globulin was to prevent the development of coronary abnormalities. We hoped also to terminate signs and symptoms of the illness promptly, thereby shortening hospitalization and decreasing the cost of treatment. The results of this pilot study confirm that intravenous infusion of gamma globulin shortens clinical illness and prevents development of coronary abnormalities in children with KD.^{6,7} The question now concerns the optimal treatment with intravenous gamma globulin—when it should be given, in what dose, and to whom.¹⁶

Pathologic studies by Fujiwara and colleagues¹⁷ of coronary arteries in this disease indicated that aneurysm formation was the extreme manifestation of a vasculitis present in the major coronary arteries even in patients without demonstrated coronary dilatation in the acute stage. If early treatment in the first week could abort this process, it

would seem worthwhile to use a large dose of intravenous gamma globulin as a single dose as soon as the diagnosis is made. Early treatment requires pediatricians to be alert to the possibility of KD in children with sustained fever and rash. We recognize the difficulty in being certain of the diagnosis before the seventh day, since some signs initially may not seem characteristic and because there is no specific diagnostic test. Although previous studies showed that gamma globulin treatment initiated before the 15th day was effective,^{6,7,18} it seems reasonable that, if possible, the treatment should be given in the first week.

This clinical trial addressed the question of dosage. One large dose early rather than four smaller doses over 4 days seemed to us to offer the possibility of quickly and favorably interrupting the sequence of symptoms, signs, and complications while decreasing the total amount of gamma globulin infused and the days of hospitalization. This concept was reinforced by the changes in *in vitro* immune function seen overnight by Leung et al.¹⁹ We selected the dose of 1 g/kg over 6 to 8 hours with the thought that it could be repeated if symptoms and signs did not rapidly improve. The flexibility of this protocol permitted us to design the treatment to match the patient's response. Twenty-seven children responded well to a single dose while five required more than one dose. No coronary artery dilatation or aneurysm developed after intravenous gamma globulin treatment, and two aneurysms, present before treatment on the sixth day, regressed by 2 weeks later. Since aspirin was given in high doses to only five patients for longer than 2 days, we think it contributed little to the favorable outcome.

We compared the results in this pilot study of consecutively treated patients with those of the multicenter, controlled study⁸ that used four daily doses of intravenous gamma globulin for a total of 1.6 g/kg (Table). Both intravenous gamma globulin protocols were significantly better than aspirin alone, and the two regimens with intravenous gamma globulin were not statistically significantly different from each other. There was a small group of patients (8%) in the controlled trial who had coronary ab-

Comparison of Treatment Regimens*			
Regimen	Total No. of Patients/ No. (%) of Patients With Coronary Abnormality		
	Before Treatment	2 wk After Treatment†	7 wk-2 mo After Treatment‡
I	78/4 (5.1)	78/18 (23.1)	79/14 (17.7)
II	75/2 (2.7)	75/6 (8.0)	79/3 (3.8)
III	32/2 (6.3)	32/0 (0.0)	32/0 (0.0)

*I indicates treatment with aspirin alone; II, aspirin plus 400 mg/kg of intravenous gamma globulin; III, aspirin plus 1 g/kg of intravenous gamma globulin.

† $P < .02$ for regimen I vs II, $P < .003$ for regimen I vs III, and not significant for regimen II vs III.

‡ $P < .01$ for regimen I vs II, $P < .01$ for regimen I vs III, and not significant for regimen II vs III.

normalities at 2 weeks and 4% at 7 weeks despite intravenous gamma globulin treatment. Although 6% of our patients had aneurysms before treatment, none did so by 2 weeks or 2 months afterward. The use of a flexible drug strategy has the advantage of allowing a second dose for less responsive patients with persistent fever, irritability, and other signs of illness.

We recognize that a proper comparison requires a controlled, randomized trial. To use historical controls in our own institution, as we did for the 110 children treated in the preceding 6 years with aspirin alone,⁴ has well-known limitations. However, the criteria for diagnosis of the disease and for echocardiographic interpretation were the same and the observers were the same throughout. The regression of aneurysms was more rapid than we had previously experienced.⁴ We believe that our pilot study of single, high-dose intravenous gamma globulin suggests enough potential benefit to warrant further study in a controlled, blinded, randomized clinical trial. Such a trial ideally should contrast with fixed-dose intravenously administered gamma globulin and determine whether aspirin plays any role at all. This will require several hundred patients.

Who should receive intravenous gamma globulin? Can those at greatest risk

be confidently selected? We analyzed risk factors for development of coronary artery abnormalities^{4,20,21} in these 32 patients to see if this would have helped us to select for early treatment in the first 7 days only those 20% to 25% of patients who would be expected to develop that complication. We had found that three laboratory findings were associated with risk: sedimentation rate greater than or equal to 100 mm/h, platelet count greater than or equal to $1 \times 10^{12}/L$, and echocardiographic evidence of pericardial effusion. Although the sedimentation rate was this elevated in 14 children, only 6 children in the first week had a value this high. In no child was the platelet count greater than $1 \times 10^{12}/L$ in the first week. The other sign, pericardial effusion,^{4,21} was present in 13 children, 11 of whom were seen and treated in the first week. These variables do not allow a reliable early selection of patients at high risk for developing coronary artery aneurysms. Therefore, we believe that treatment with intravenous gamma globulin should be given to all children with acute KD.

While we have concentrated on the most common cardiac sequela, the coronary artery disease, it is also true that valvular heart disease in the form of mitral and aortic regurgitation did not occur in this group of patients.

What did it cost to prevent the serious

complications of KD? The cost of one course of 1 g/kg of gamma globulin was less than the cost for the 4-day course of 400 mg/kg daily. Furthermore, the median hospital stay of 4 days was shorter with the single-dose protocol even though five children needed a second course and a longer stay. Therefore, intravenous gamma globulin given in a flexible regimen beginning with a single dose of 1 g/kg may not only prevent development of coronary artery aneurysms but also "pay for itself" by shortening illness and hospitalization. The cost to the child who develops coronary artery disease and to his or her family as well as to society is enormous in comparison to the cost of giving gamma globulin to all children with acute KD.

CONCLUSIONS

We conducted a clinical trial as a pilot study in children with acute KD, using a single dose of 1 g/kg of intravenous gamma globulin. We found it to be effective in 27 of 32 patients. The other 5 patients had an equally good result after a dose that ranged from 1.5 to 3 g/kg. This regimen terminated the signs and symptoms of illness and prevented coronary artery and valvular complications. Despite the limitations of a one-arm, uncontrolled study, we believe that this treatment protocol has both medical and economic benefits and should be further evaluated.

We are grateful for the cooperation of the pediatric cardiology fellows and the pediatric house staff at Cornell University Medical College, New York, NY, in carrying out this protocol. We acknowledge with appreciation the contributions to this study of Kathryn H. Ehlers, MD, and June Robins of the echocardiography laboratory and of Ethel Longo, Rebecca Campbell, Brina Ellis, Denise Simonette, and Lydia Rosario of the graphics laboratory; Sylvia Carnazza, research student; Ginette Lanois, hematology technician; as well as the nursing care provided by Julie Fitzgerald-Pedersen, RN, and Mickey Miceli, RN. We thank Linda Rasoulnejad for assistance in follow-up of patients, Shiela Reams for help with statistics, and Trish Simmons for manuscript preparation.

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Book Review

Child Sexual Abuse: A Handbook for Health Care and Legal Professionals, by D. H. Schetky and A. H. Green, 264 pp, \$27.50, New York, NY, Brunner/Mazel Publishers, 1988.

Child Sexual Abuse, A Handbook for Health Care and Legal Professionals is an excellent resource for the professional interested in improving his or her database and skills in caring for sexually abused children. This concise volume, less than 300 pages, is readable and well referenced. As the excerpt below illustrates, the introduction begins with some interesting cultural comments regarding child sexual abuse in general and incest in particular:

Sociological reasons for the [incest] taboo stem from the need to strengthen the tribe through new alliances. This was very simply and eloquently stated to Margaret Mead by an elderly member of the Arapesh of New Guinea, who replied in response to her query about incest, 'What, you would like to marry your sister! Don't you want a brother-in-law? Don't you realize that if you marry another man's sister and another man marries your sister, you will have at least two brothers-in-law while if you marry your own sister you will have none? With whom will you hunt, with whom will you garden, whom will you visit?'

The authors divided their book into these sections: overview, which includes a review of normal psychosexual development and historical perspectives; evaluations; legal issues; and treatment and prevention. At the end is an extensive appendix of references and educational materials with many useful authors' comments.

The clinical evaluation of child sexual abuse discussed in chapter 4 is a succinct but thorough description of what an

appropriate evaluation entails. An adequate and timely evaluation requires considerable skill and knowledge, and the authors clearly outline the pitfalls and milestones involved in completing the task. In view of the demands of this type of evaluation it is clear that practitioners who are unwilling or unable to perform such detailed assessments should be prepared to refer them to individuals who are skilled and experienced in such evaluations.

A good overview of what is involved in the medical evaluation of these patients is covered in chapter 5. Practitioners should consider this chapter a springboard for more study. For example, the authors correctly note that different positions may be used to examine a child who has been sexually abused. However, physicians need to be aware that the same genital structures may have significantly different measurements in different positions. Examiners need experience and training to interpret findings correctly. The chapters that deal with the child and the expert as witnesses are very informative. Finally, the last two chapters, on treatment and prevention, give a good summary of current practice and theory in these areas.

The authors have addressed a complex and difficult subject well, and have compiled a concise and useful body of knowledge. *Child Sexual Abuse* will be of interest to professionals in many disciplines who serve these unfortunate children and their families.

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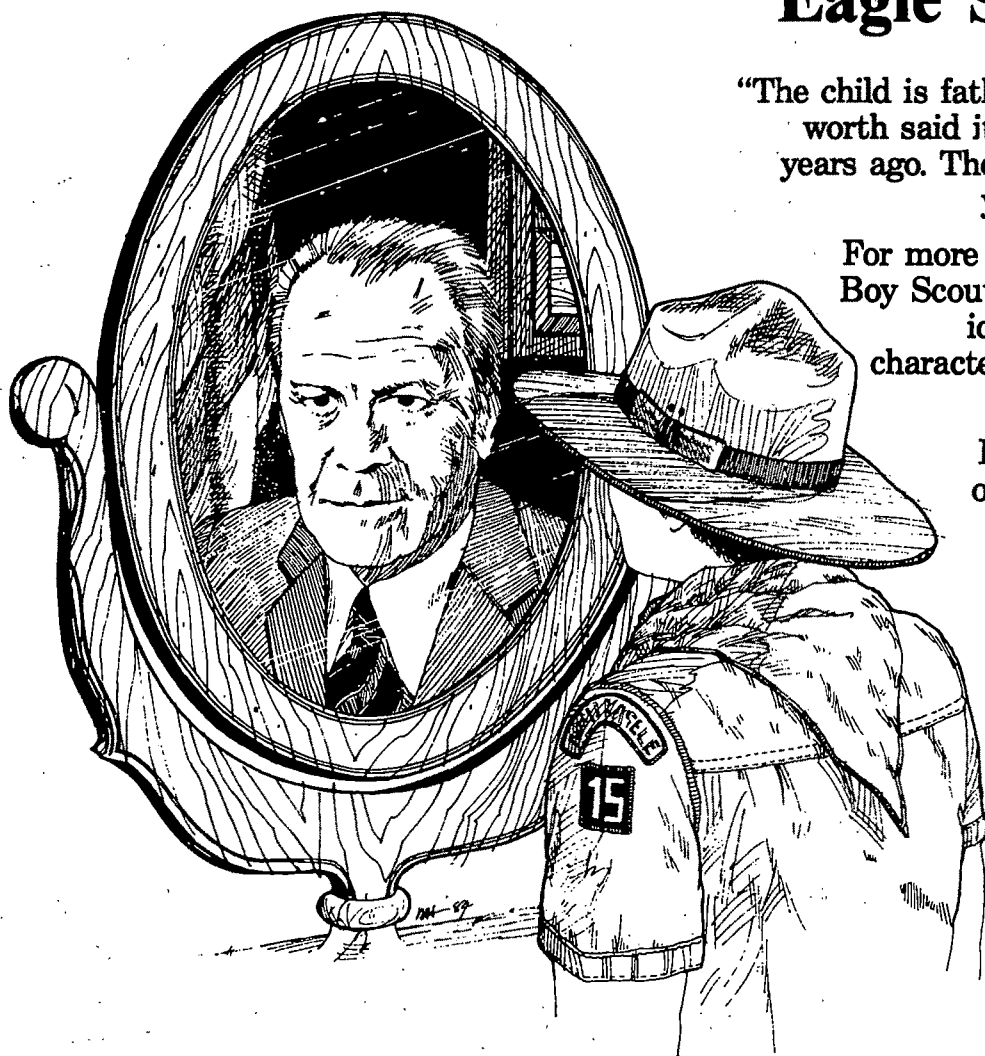
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Antiviral Drugs in Pediatrics

Henry H. Balfour, Jr, MD, Janet A. Englund, MD

• Pediatricians are made familiar with antiviral drugs and are provided with specific recommendations for treatment of viral diseases. The antiviral drugs in clinical use today are discussed in terms of their doses, routes of administration, mechanisms of action, established and potential efficacies, and toxicities. These drugs include acyclovir, amantadine, trisodium phosphonoformate, ganciclovir, ribavirin, rimantadine, vidarabine, and zidovudine. Biologic response modifiers, such as interferons, are mentioned briefly in their historical context. Future trends in antiviral therapy are anticipated with mention of the most promising candidate compounds currently in preclinical trials.

(AJDC. 1989;143:1307-1316)

Treatment of viral infections was once considered one step removed from witchcraft. Progress in antiviral therapy was impeded by the scarcity of dependable and rapid viral diagnostic techniques coupled with the misconception that all children must endure viral infections because the therapy was worse than the illness. Fortunately, that situation has changed. Due to the recent proliferation of clinical virology laboratories, it is now possible for nearly every physician to obtain laboratory confirmation of a viral diagnosis, and numerous carefully controlled clinical trials have dispelled the myth that the treatment is worse than the disease. Indeed, antiviral therapy should now be an integral part of today's practice of pediatrics. How did that come about, where are we now, and where might we be going in the future?

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THE ADVENT OF ANTIVIRAL THERAPY

The difficulty of propagating viruses in the laboratory and the lack of suitable techniques to work with viral genes and their products were the basic reasons for the slow development of antiviral drugs in the 1950s and 1960s. The antiviral effort looked even more feeble when compared with the rapid growth of antibacterial therapy. Despite technical limitations, investigators still were able to make progress in the treatment of viral infections by taking two different approaches: chemotherapeutic and immunologic. The chemotherapeutic approach aims to develop drugs that block specific steps in viral replication. The immunologic approach concentrates on compounds that enhance the host's immune defense against viral infection. Such compounds are called biologic response modifiers because they exert their activity through the host's immune system rather than directly affecting the events of viral infection and replication.

Drugs active against smallpox, known as thiosemicarbazones, represent the first chemotherapeutic agents used successfully to prevent a human viral disease. However, the global eradication of that scourge relegated this early work in antiviral chemoprophylaxis to obscurity. Hamre and colleagues¹ reported in vitro activity for two thiosemicarbazones against vaccinia in embryonated hens' eggs and mice in 1950. A decade later, isatin thiosemicarbazone was shown to protect mice from the intracerebral inoculation of a strain of smallpox.² Three years after that, in 1963, Bauer and colleagues³ demonstrated that a thiosemicarbazone could prevent smallpox in humans. These compounds were tested for antiviral effects simply because they were active against another infectious agent, *Mycobacterium tuberculosis*. Their mechanism of action against pox viruses

was never completely elucidated but appeared to be interference with the production of a late viral structural protein.⁴

A second class of antiviral drugs, the caged carbocyclics, was developed and tested in the 1960s. In 1961, Jackson and his colleagues⁵ provided convincing evidence that amantadine prevented influenza A. Yet, a quarter of a century later, amantadine is still not generally utilized as an effective antiviral compound because of its narrow therapeutic index, limited spectrum of action, and minimal effectiveness unless given during the first few days of illness. Amantadine will be discussed further in the section on influenza.

In the early 1970s, anticancer drugs were reported to be of benefit for treatment of serious viral diseases, but these open-label studies were later refuted. For example, reports that idoxuridine was useful for treatment of herpes encephalitis⁶ and that cytarabine was therapeutic for herpes zoster^{7,8} were ultimately discredited. Idoxuridine did not reduce the amount of virus in brain tissue in patients with herpes encephalitis and was far too toxic for systemic administration.⁹ Immunosuppressed patients given cytarabine for treatment of herpes zoster fared worse than those who received placebo,¹⁰ which underscored the necessity for carefully designed placebo-controlled trials to evaluate antiviral drugs. Such studies were subsequently conducted by Whitley and colleagues,¹¹⁻¹³ whose multicenter, randomized, placebo-controlled trials established the therapeutic efficacy of vidarabine for treatment of serious herpes group viral infections. These exemplary studies became the yardstick against which the utility of subsequent antiviral compounds was measured.

In the 1970s, the interferons emerged as promising biologic response modifiers for treatment of viral infections.¹⁴ Interferons were especially attractive because of their broad spectrum of anti-

viral activity. It is now known that interferons are proteins of at least three distinct types: alpha, beta, and gamma. These proteins, which are coded for by the host, do not act directly on viruses but require the cellular synthesis of both RNA and protein to be active. Once interferon is produced by cells, it is released and functions like a hormone: it binds to specific and nonspecific receptors at the plasma cell membrane, is internalized, and alters cellular enzymatic activities so that production of viral proteins is reduced. Early clinical trials utilized human leukocyte interferon, whereas interferons made from recombinant or purified sources have been recently tested for treatment of a number of unrelated human viral diseases. Unfortunately, an ill-defined mechanism of action and frequent influenzalike side effects have hampered the clinical application of interferons and their inducers.

The past has taught us that specific obstacles need to be overcome to develop clinically useful chemotherapeutic agents or biologic response modifiers. Some of the major hurdles follow:

1. The expression of viral diseases is variable, making carefully designed, randomized, controlled clinical trials mandatory.
2. Clinical and laboratory end points used to determine antiviral effects are not standardized and are often indistinct.
3. The presence or promise of viral vaccines dampens the enthusiasm to develop antiviral therapy.
4. The commercial value of candidate antiviral drugs is questionable, especially if their use benefits only a small group of patients, such as bone marrow allograft recipients.

Despite these obstacles, the era of antiviral therapy has dawned. In this review, we will concentrate on the chemotherapeutic drugs currently in clinical use (Table 1). Antiviral compounds will be discussed in the context of their clinical indications; biologic response modifiers are mentioned briefly where appropriate.

ANTIVIRAL DRUGS: THE PRESENT Herpes Simplex Virus Infections

Substantial advances have been made in this decade against infections caused

by herpes simplex virus types 1 and 2. Indeed, more treatment trials have been designed for herpes simplex virus infections than for any other human viral disease. There are several reasons for this intense scientific scrutiny: herpes simplex virus infections may have serious consequences, particularly in immunocompromised hosts; the virus grows well in many cell culture systems; and herpetic lesions are easily recognized, and, thus, progression to healing can be closely monitored during clinical trials. Nevertheless, some of the most common herpetic infections have not yet been studied in controlled clinical trials, and the optimum dosages of antiviral drugs for other herpes diseases have yet to be established.

Two drugs have been proved effective for treatment of systemic herpes simplex virus infections: vidarabine and acyclovir. Vidarabine, which acts at multiple sites in the viral replicatory cycle, does not require a virus-encoded enzyme to be converted to the active state, vidarabine triphosphate. Vidarabine triphosphate is both a competitive inhibitor of and faulty substrate for viral DNA polymerase; it also inhibits several steps in viral RNA synthesis, including capping of viral messenger RNA.¹⁵ The compound is rapidly degraded by adenosine deaminase to vidarabine hypoxanthine, a derivative with much less antiviral activity than its parent. Because vidarabine is poorly absorbed orally and is relatively insoluble, it must be given intravenously in a relatively large volume of 5% dextrose solution. A disadvantage of vidarabine is its potentially severe central nervous system toxicity.¹⁶

Acyclovir, an acyclic analogue of guanosine, must be phosphorylated to acyclovir triphosphate to exert its antiviral activity.¹⁷ The metabolism of acyclovir to acyclovir monophosphate is accomplished by a virus-specified deoxynucleoside kinase commonly called thymidine kinase (TK). Acyclovir is then further phosphorylated to acyclovir triphosphate by host cell enzymes. Like vidarabine triphosphate, acyclovir triphosphate is both an inhibitor of and a faulty substrate for viral DNA polymerase. Acyclovir triphosphate is also an inhibitor of cellular DNA polymerase, but very little acyclovir triphosphate is

generated in uninfected mammalian cells. Therefore, acyclovir exerts minimal inhibition on cellular alpha-DNA polymerase in uninfected cells, which is the major reason for its low toxicity. However, uncommon adverse effects or sequelae resulting from long-term use of acyclovir in children have not been completely ruled out, because acyclovir has been in clinical use for a relatively short time.

The other antiherpes drugs licensed only as topical ophthalmic preparations are idoxuridine and trifluridine, which are both nucleosides that inhibit viral DNA polymerase. They are effective topically but are too toxic for systemic administration. Both ganciclovir and trisodium phosphonoformate (Foscarnet) are active against herpes simplex viruses *in vitro*, but are not licensed in the United States at the present time for children and cannot be recommended for routine use in herpes infections because acyclovir is less toxic and easier to administer.

Herpes Keratitis.—This is the only viral disease for which we have the luxury of three topical treatment options: idoxuridine, vidarabine, or trifluridine. Acyclovir ophthalmic ointment is available in some countries, but not the United States. When is it appropriate to treat a child with herpes keratitis systemically rather than topically? Systemic therapy is recommended for infants under the age of 1 month or for patients who have a generalized herpetic infection manifested by mucosal and cutaneous lesions. Herpes keratitis occasionally precedes encephalitis, and, therefore, any patient who shows signs of central nervous system dysfunction should be treated systemically.¹⁸

Neonatal Herpes.—This is one of the most devastating viral infections confronting pediatricians. The incidence of neonatal herpes in the United States is about 1 in 8000 live births.¹⁹ Recent controlled clinical studies have suggested that early therapeutic intervention is necessary to minimize morbidity.^{18,20} A trial of vidarabine vs acyclovir did not prove either medication to be clearly superior.²¹ We prefer acyclovir because of its better solubility in intravenous fluids, the availability of an oral formulation, and greater efficacy for treatment of most types of herpetic infec-

Table 1.—Antiviral Drugs in Clinical Use (Excluding Antiretroviral Drugs)*

Generic Name	Tradename	Target Viruses	Route of Administration	Dose	Frequency	Days of Therapy	Major Toxicity
Acyclovir	Zovirax	Herpes group	Topical, oral, IV	See Table 2	See Table 2	See Table 2	Renal (IV only)
Amantadine	Symmetrel	Influenza A	Oral	2.2-4.4 mg/kg†	Every 12 h	5	CNS
Ganciclovir	Cytovene	Cytomegalovirus	IV	2.5 mg/kg	Every 8 h	14	Bone marrow
Idoxuridine	Stoxil, Herplex	Herpes simplex	Topical ophthalmic	Varies, see package insert	...	≤21	Local irritation
Ribavirin‡	Virazole	RSV; influenza§	Aerosol	6 g in 300 mL H ₂ O given over 16-20 h	Every 24 h	5	...
			Oral,§ IV§	Not determined	Anemia
Rimantadine§	Not determined	Influenza A	Oral	3.3 mg/kg	Every 12 h	5	CNS
Trifluridine	Viroptic	Herpes simplex	Topical ophthalmic	1 drop	Every 2 h while awake	≤21	...
Trisodium phosphonoformate‡§	Foscarnet	Cytomegalovirus	IV	Under investigation	Every 8 h	14	Renal
Vidarabine	Vira-A	Herpes simplex	IV	15-30 mg/kg infused over 12 h	Every 24 h	10	CNS
			Topical ophthalmic	1.25 cm of ointment	Every 3 h while awake	≤21	...

*IV indicates intravenous; CNS, central nervous system; and RSV, respiratory syncytial virus.

†Reduce dose on renal failure according to package insert.

‡See also Table 3.

§This is not a licensed indication or formulation in the United States.

tions. To assure a better outcome for the child, however, our diagnostic skills need to be improved and the optimum dosage of antiviral drugs firmly established. Because treatment of the infant may not be instituted in time to prevent brain damage, the administration of acyclovir to "high-risk" mothers before delivery is being investigated.

Acyclovir appears to be safe and effective in healthy term newborns with normal renal function. Because approximately 80% of acyclovir administered intravenously is eliminated by the kidneys, the dose must be adjusted according to creatinine clearance. Peritoneal dialysis and blood exchange transfusions, unlike hemodialysis, do not remove an appreciable amount of acyclovir.²² If available, acyclovir levels are useful for monitoring therapy in premature infants and infants in renal and/or hepatic failure. Our recommendations for acyclovir dosages in children, including infants and patients with compromised renal function, are given in Table 2.

Herpes Gingivostomatitis.—The typical child with primary herpes gingivostomatitis does not need antiviral treatment. If children are so uncomfort-

able that they stop drinking and require hospitalization for parenteral fluids, it is reasonable to give them intravenous acyclovir. Some pediatricians elect to treat ambulatory patients who have a relatively severe episode of either primary or recurrent oral herpes. In such instances, we recommend oral acyclovir. The only oral acyclovir formulation presently available in the United States is a 200-mg capsule. When treating toddlers, the capsules can be opened and their contents mixed with either applesauce or fruit juice. Domestic licensure of an oral acyclovir suspension (200 mg/5 mL) is pending and, once approved, will make oral administration for young children much easier. Older children often report having a sensory prodrome prior to the eruption of oral herpes. If therapy is elected, it should be instituted as soon as the prodrome is felt and continued until the lesions crust. Long-term suppressive therapy for oral herpes in children is not recommended.

Herpes Whitlow.—Herpes whitlow frequently results when children with oral herpes suck their fingers. If therapy is elected, these patients must be treated with oral or intravenous acyclovir because herpetic whitlow involves

subcutaneous tissues and will not respond to topical acyclovir.²³

Genital Herpes.—Primary genital herpes is often a significant clinical illness that requires either intravenous or oral acyclovir. Pediatricians should consider the possibility of sexual abuse in young patients with genital herpes. Patients should be counseled about the possibility of recurrences. Episodes that are not associated with systemic symptoms and occur infrequently do not need to be treated unless these recurrences are psychologically intolerable. Patients with frequent recurrences (six or more per year) will benefit from suppressive therapy. If suppressive therapy is elected, we recommend that it be discontinued for several months approximately every 6 months to reevaluate its need. Most patients can be weaned off acyclovir after 6 months to 2 years. Although lesions may recur following discontinuation of suppressive therapy, a recent clinical trial has confirmed the adage that "the severity and frequency of recurrences of genital herpes diminish with time."²⁴ Alternatively, early patient-initiated therapy of recurrences at the onset of symptoms may be effective in older children.

Table 2.—Acyclovir Dosage Recommendations for Children*

Indication	Underlying Condition	Route of Administration	Amount per Dose, mg/kg	Frequency of Dose	Duration, d
Herpes simplex virus Neonatal herpes	Term newborn	IV	10	Every 8 h	14-21
	Premature infant	IV	10	Every 8-12 h	14-21
Encephalitis	Otherwise normal	IV	10	Every 8 h	10-14
Mucocutaneous herpes	Immunocompromised or hospitalized for fluids	IV	5	Every 8 h	5-7
Herpes infections in renal failure	CrCl, 0.42-0.83 mL/s	IV	10	Every 8 h	7
	CrCl, 0.17-0.42 mL/s	IV	10	Every 24 h	7
	CrCl, <0.17 and hemodialysis	IV	10	Every 48 h	7
	Continuous peritoneal dialysis	IV	5	Every 24-48 h	7
	Double-volume blood exchange	IV	5	Every 24-48 h	7
Varicella-zoster virus† Varicella	Immunocompromised	IV	10	Every 8 h	7
	Otherwise normal	Oral		Under investigation	
Herpes zoster	Immunocompromised	IV	7.5	Every 8 h	5-7
	Otherwise normal	Oral	20‡	Every 6 h	5
Epstein-Barr virus†	Immunocompromised with lymphoproliferative syndrome	IV	10	Every 8 h	10-14
Cytomegalovirus prophylaxis†	Immunocompromised	IV	10	Every 8 h	36
		Oral	20‡	Every 6 h	90

*IV indicates intravenous; CrCl, creatine clearance.

†These recommendations are the authors', not a Food and Drug Administration-approved indication.

‡Maximum dose, 800 mg.

Herpes Encephalitis.—Herpes should be suspected in any child with focal encephalitis. Fortunately, herpes simplex encephalitis is rare in pediatrics, but it is impossible to distinguish herpetic from nonherpetic encephalitis in an individual patient.²⁵ In the past, therefore, a brain biopsy was advocated prior to institution of therapy. Acyclovir has been demonstrated to be superior to vidarabine for the treatment of herpes simplex encephalitis in adults.²⁶ Because the toxicity and tolerance profile of acyclovir for this disease is quite favorable, the need for a brain biopsy before treatment is now questionable. Treatment that is instituted without a biopsy, however, is empiric because the diagnosis of herpes simplex encephalitis cannot be confirmed without a brain biopsy. Patients whose condition deteriorates despite acyclovir therapy will require aggressive neurodiagnostic evaluation including a brain biopsy.²⁷

Mucocutaneous Herpes in Immunocompromised Children.—Acyclovir is clearly indicated for this disease, but there are two choices in patient management. Acyclovir may be given prophylactically during a known period of immunosuppression, such as immediately

before and after bone marrow transplantation.²⁸ A second approach is to monitor patients closely following transplantation or induction chemotherapy and to treat those who develop symptomatic herpetic infections. Unfortunately, subtherapeutic use of acyclovir (usually intermittent oral dosing) has been associated with emergence of resistant herpes simplex virus strains.^{29,30} As we care for more and more pediatric patients with acquired immunodeficiency syndrome (AIDS), viral resistance to acyclovir could become widespread.

Herpes Simplex Viruses Resistant to Acyclovir.—Acyclovir-resistant herpes group viruses are rarely found in otherwise-normal hosts, but have been reported in immunosuppressed patients, such as bone marrow transplant recipients or persons with AIDS.^{29,30} At least three mechanisms are responsible for the development of resistance to acyclovir by herpes simplex virus strains. The first is loss of the ability to induce TK. Herpes simplex viruses that do not induce TK, called TK-negative strains, may account for about 0.1% of herpes simplex viruses found in patients' lesions. These strains are the

most common form of resistant herpes simplex viruses encountered in clinical practice. The other two kinds of resistant herpes simplex virus strains are rarely grown from cultures taken from patients. Resistant herpes simplex strains have been described that induce TK in infected cells, but the enzyme has altered specificity such that it does not phosphorylate acyclovir. Herpes simplex mutants resistant to acyclovir due to an alteration in DNA polymerase have also been described. These viruses are of concern because they have the potential to be resistant to antiviral compounds unrelated to acyclovir, such as trisodium phosphonoformate. Laboratory strains of herpes simplex with a combination of DNA polymerase and TK alterations have also been characterized. In addition to resistant herpes simplex viruses, strains of varicella-zoster virus³¹ and cytomegalovirus³² have developed resistance to acyclovir or ganciclovir in certain circumstances.

Varicella-Zoster Virus Infections

Varicella vaccine³³ will probably be licensed in the United States soon, but it

is highly unlikely that enough children will be vaccinated to achieve herd immunity for years to come. Reactivation of varicella-zoster virus as shingles will continue to keep this virus circulating in the community for a long time after the majority of children have been immunized, and vaccine failures, especially in immunocompromised children, are to be expected.³⁴ Therefore, therapy for varicella-zoster virus infections is definitely needed.

Varicella-Zoster Virus Infections in the Immunocompromised Host.—Because the risk of visceral dissemination and death from varicella-zoster virus infections in immunosuppressed hosts is high compared with that in normal children, early treatment trials focused on immunocompromised patients. Both vidarabine and acyclovir have been shown to decrease the rate and severity of complications from varicella-zoster infections.^{11,35} We recommend acyclovir because it has proved to be superior to vidarabine in two comparative trials.^{36,37} Varicella-zoster virus codes for TK, and acyclovir triphosphate inhibits varicella-zoster virus DNA polymerase in infected cells. However, varicella-zoster virus is 4 to 10 times less sensitive to acyclovir than herpes simplex virus, and, therefore, a higher dose is needed to treat varicella-zoster infections (Table 2). Like herpes simplex virus, resistant TK-negative varicella-zoster virus strains may be selected for by suboptimal therapy.³¹

Varicella in Otherwise-Normal Children.—Approximately 3.5 million persons develop varicella in the United States each year, resulting in the hospitalization of at least 4000 previously healthy children.³⁸ An effective therapy would be appropriate as an alternative to immunization or for treatment of vaccine failures. The use of an oral suspension of acyclovir for the treatment of varicella in otherwise-healthy children is currently being investigated.

Herpes Zoster in Otherwise-Normal Children.—Acute pain and postherpetic neuralgia are less severe in children than adults. However, some children with localized dermatomal herpes zoster are quite uncomfortable and would benefit from acyclovir therapy if it is started early in the course of the disease. Both intravenous³⁹ and oral⁴⁰ acy-

clovir have been shown to lessen the period of acute pain and hasten cutaneous healing in adults. One study has also shown that oral acyclovir reduced the rate of postherpetic neuralgia.⁴¹

Epstein-Barr Virus Infections

Because Epstein-Barr virus does not induce TK in infected cells, very little acyclovir is phosphorylated. However, Epstein-Barr virus DNA polymerase is quite sensitive to acyclovir and the small amount of acyclovir triphosphate phosphorylated by naturally occurring host cell enzymes may be sufficient to produce an antiviral effect.

In contrast to the therapeutic benefit of acyclovir in herpes simplex and varicella-zoster virus infections, treatment trials for Epstein-Barr virus infections have met with little success.⁴² This is probably because the most common manifestation of Epstein-Barr virus infection, infectious mononucleosis in the otherwise-normal host, results from injury induced by the immune response to Epstein-Barr virus rather than by active viral replication. Thus, an antiviral drug that limits viral replication usually is introduced too late in the course of clinical illness to affect the immune-mediated symptom complex. Such may not be the case for immunocompromised patients in whom a longer period of viral replication may precede clinical deterioration. The posttransplant lymphoproliferative syndrome, an unusual result of ongoing Epstein-Barr virus replication, appears to respond either to acyclovir or reduction in immunosuppression unless it has degenerated into a monoclonal malignant tumor.⁴³ Once cellular transformation or chromosomal alteration/integration has occurred, the tumor would not be expected to regress when treated with an antiviral drug. Hairy leukoplakia in patients with AIDS, a condition attributed to Epstein-Barr virus, also has been observed to respond to acyclovir.⁴⁴

Cytomegalovirus Diseases

Cytomegalovirus is the most pernicious of all the herpes group viruses. While some progress has been made in the prevention and treatment of cytomegalovirus infections in immunocompromised patients, congenital cytomegalovirus infections have not yet been shown to respond to antiviral drugs.

Congenital Cytomegalovirus Infections.—Investigators have attempted to treat congenital cytomegalovirus infections with anticancer drugs, vidarabine, and acyclovir but found no clinical benefit.⁴⁵⁻⁴⁷ It is possible that children who have milder forms of congenital cytomegalovirus infection would benefit from antiviral intervention because sensorineural hearing loss or attention deficits develop slowly after birth. Studies with ganciclovir are planned for this group of patients under the auspices of the National Institutes of Allergy and Infectious Diseases (Bethesda, Md) Antiviral Study Group.

Cytomegalovirus Infections in the Immunocompromised Host.—Two major recent advances have been made in the management of cytomegalovirus infections in immunocompromised patients. The first is the development of ganciclovir, an acyclovir derivative with increased activity against cytomegalovirus as compared with the parent compound.⁴⁸ Unlike acyclovir, ganciclovir is readily metabolized to ganciclovir triphosphate in cells infected with cytomegalovirus. Ganciclovir triphosphate is a competitive inhibitor and faulty substrate for cytomegalovirus DNA polymerase. The average inhibitory dose of ganciclovir for cytomegalovirus strains is 2.5 $\mu\text{mol/L}$ as compared with 63 $\mu\text{mol/L}$ for acyclovir.⁴⁹

No rigorously controlled clinical trials with ganciclovir have been published, but abundant data attest to its *in vivo* antiviral effect. Ganciclovir appears to be the best drug for the treatment of established cytomegalovirus disease in immunocompromised adults. Ganciclovir is given intravenously because of poor oral bioavailability. White blood cell counts should be closely monitored because neutropenia is a common side effect. Neutropenia can be alleviated by dose reduction or temporary cessation of therapy. A retrospective review of 12 pediatric patients by Gudnason et al⁵⁰ suggests that the effect of ganciclovir in children is similar to that of adults. To qualify for experimental therapy with ganciclovir, a patient must have sight-threatening or life-threatening cytomegalovirus disease documented by retinal examination or biopsy of the involved organ.

The second major advance in the management of cytomegalovirus disease in the immunocompromised host is acyclovir prophylaxis. Cytomegalovirus does not induce TK in infected human cells, but its DNA polymerase, like that of Epstein-Barr virus, is very sensitive to acyclovir triphosphate. The small amounts of the triphosphate produced in infected cells may be sufficient to prevent initiation of viral replication. Meyers et al⁶¹ demonstrated that intravenous acyclovir prevented cytomegalovirus infection and disease in seropositive bone marrow allograft recipients who received drug treatment for 36 days beginning 5 days before transplantation. These results have been confirmed and extended by Balfour et al,⁶² who performed a randomized, placebo-controlled, double-blind protocol of high-dose oral acyclovir in 104 renal allograft recipients. Acyclovir was well tolerated, even in the immediate post-transplant period, and significantly reduced the rates of cytomegalovirus infection and disease, especially in antibody-negative recipients whose donors were seropositive.

Because acyclovir can prevent cytomegalovirus disease, children who have just undergone a transplant operation and are seropositive for cytomegalovirus or who are seronegative but receive a solid organ from an antibody-positive donor might benefit from a course of prophylactic oral acyclovir (Table 2). Those who develop cytomegalovirus disease despite acyclovir prophylaxis should be treated with ganciclovir.

Immune serum globulin preparations are presently being investigated for prevention and treatment of cytomegalovirus disease. While immunoglobulin has been shown to have a prophylactic effect,⁶³ the data on treatment efficacy are not clear. There is some evidence that cytomegalovirus pneumonitis in bone marrow transplant patients is immunologically mediated and that the immune damage could be blocked by infusing cytomegalovirus antibodies.⁶⁴⁻⁶⁶ Further confirmation of this observation is required before immunoglobulin preparations can be endorsed as part of the treatment regimen for cytomegalovirus infections in marrow transplant patients. Cytomegalovirus immune globulin should not be used alone for

management of cytomegalovirus pneumonia in transplant recipients or patients with AIDS. The compelling evidence for active replication of cytomegalovirus in the lungs of these patients is the rationale to include ganciclovir in the treatment regimen.

Trisodium phosphonoformate is an attractive future candidate for treatment of cytomegalovirus disease because it is structurally different from both acyclovir and ganciclovir. Hence, viruses resistant to those nucleoside analogues should still be sensitive to trisodium phosphonoformate. Trisodium phosphonoformate treatment of cytomegalovirus disease in patients who have undergone transplants has produced encouraging preliminary results,⁶⁷ and controlled studies are planned in allograft recipients.

Respiratory Viral Infections

The development of specific therapy for respiratory viral infections was impeded for many years by the lack of reliable and rapid diagnostic techniques. Today, viral antigen assays can be performed directly on clinical specimens, or after viruses have been in cell culture for less than a day. Thus, a specific viral diagnosis can be provided quickly, making antiviral therapy practical.

Respiratory Syncytial Virus.—Considered the most important cause of bronchiolitis and pneumonitis in young children, respiratory syncytial virus is responsible for significant mortality in infants with underlying cardiac, pulmonary, or immune defects. Ribavirin, a broad-spectrum antiviral agent first synthesized in the 1970s, has been shown to inhibit replication of respiratory syncytial virus, influenza, parainfluenza, and numerous other viruses. The mechanism of action of ribavirin is not precisely known. This drug appears to interfere with steps in the capping and elongation of messenger RNA, although some antiviral effect may be due to reduction of guanine nucleosides following feedback inhibition of cellular inosine monophosphate dehydrogenase.^{68,69}

The advent of rapid and reliable diagnostic techniques for respiratory syncytial virus and a novel method of administration— aerosolization— have

triggered renewed interest in the potential treatment of respiratory syncytial virus disease. Ribavirin administered as a small-particle aerosol was shown to be rapidly deposited throughout the respiratory tract in concentrations sufficient to inhibit respiratory syncytial virus. Placebo-controlled clinical trials in a small number of patients at several medical centers have demonstrated a degree of efficacy for aerosolized ribavirin therapy in infants with respiratory syncytial virus infections.^{60,61} In one study, a dose of ribavirin administered by aerosol approximately 20 hours per day resulted in a reduction in viral load and clinical improvement.⁶⁰ Although transient anemia and elevated levels of bilirubin have been reported after oral or intravenous administration, aerosolized ribavirin has been consistently free of adverse effects.

The recent licensure of ribavirin for the treatment of respiratory syncytial virus disease has made pediatricians more aware of the utility of antiviral therapy. However, a clear consensus of who should receive ribavirin therapy has not been reached. This is partially due to the high cost of ribavirin administration (roughly \$500 to \$700 per day) and the lack of controlled studies containing substantial numbers of subjects. The decision to treat a patient with ribavirin aerosol should be based on the severity of respiratory syncytial virus disease and the child's general health. Most infants and children with respiratory syncytial virus infection have a mild, self-limited disease that does not require hospitalization or antiviral therapy. However, premature infants or children with underlying cardiac or pulmonary disease or immunodeficiency are at high risk for respiratory syncytial virus-related complications and should be considered for early therapy, even if their disease initially appears to be mild. Seriously ill children who may require assisted ventilation, such as those whose PaO₂ is less than 65 mm Hg or whose PaCO₂ is rising, have also been proposed as candidates for ribavirin treatment.^{62(pp528-530)} Although problems have been associated with the use of ribavirin in ventilators and the drug is not licensed for use during mechanical ventilation, some investigators suggest that ribavirin can be safely and effec-

tively administered by trained personnel who carefully monitor ventilator pressure and frequently change on-line filters to anticipate and prevent drug precipitation and plugging.⁶³

Ribavirin is contraindicated in pregnant women because it is teratogenic in rodents, although not in primates. Concern exists about possible exposure of hospital personnel to ribavirin while caring for patients receiving the aerosolized drug. The actual risk of ribavirin exposure to health care workers is uncertain. One study did not detect ribavirin in nurses who worked for 3 days with infants being treated.⁶⁴ In another study, ribavirin was detected in the erythrocyte fraction in 1 of 30 blood specimens obtained from 10 health care workers who had been in close contact with patients.⁶⁵ This latter study demonstrated minimal environmental contamination from intubated patients vs those who received the drug by oxygen hood or face mask. Calculations designed to demonstrate possible teratogenic levels of ribavirin based on concentrations of drug derived from air sampling techniques in this study are open to question, however. Because the basis of ribavirin-induced teratogenicity in rats is not understood, it would be prudent for hospital personnel who are pregnant or contemplating pregnancy to avoid working directly with patients receiving aerosolized ribavirin.

Influenza.—Antiviral agents for the prophylaxis and treatment of influenza infections are among the oldest drugs in our antiviral armamentarium. Amantadine, a synthetic caged carbocyclic compound, was licensed in 1966 for the prevention and treatment of the H2N2 strain of influenza A, and in 1976 for treatment of all strains of influenza A. Amantadine is thought to exert its antiviral activity by interfering with uncoating of the virus or the primary transcription of viral RNA.⁶⁶ When given shortly after onset of illness, it has been shown to reduce the incidence and severity of illness in otherwise-healthy adults.⁶⁷ Amantadine therapy should be considered for unvaccinated high-risk patients who develop an influenzalike illness during community-wide influenza A outbreaks. Prophylaxis should be considered during influenza epidemics in children who cannot be immunized or

who are exposed less than 14 days following immunization. Children who are candidates for amantadine prophylaxis include those with pulmonary disease, such as bronchopulmonary dysplasia, asthma, or cystic fibrosis, and those with chronic cardiac, renal, hematologic, or immunologic dysfunction.^{62(pp243-251)}

Because oral amantadine is well absorbed and 90% of the dose is excreted unchanged in the urine, the dose should be reduced in patients with renal insufficiency according to the package insert. Amantadine therapy has been associated with central nervous system side effects, including insomnia, lightheadedness, and difficulty concentrating, although these symptoms disappear when the drug is discontinued. Amantadine is contraindicated in patients with seizure disorders.

Rimantadine hydrochloride, an amantadine analogue widely used in the Soviet Union, has been reported to be as effective as the parent compound against influenza A viruses *in vivo*.⁶⁸ Fewer central nervous system side effects have been reported as compared with amantadine. Gastrointestinal disturbances occurred in approximately 2% of children in two studies.^{69,70} Viruses resistant to amantadine and rimantadine have been reported, but their clinical significance is not yet known.⁷¹ Food and Drug Administration licensure of rimantadine is anticipated shortly.

Parainfluenza.—Parainfluenza viruses have been associated with nearly 25% of acute respiratory infections in day-care centers and appear to be the major culprits in croup and lower respiratory tract diseases in children under the age of 2 years. Although ribavirin has reasonable *in vitro* activity against parainfluenza, clinical data on its use for the treatment of parainfluenza disease have not been published.

Rhinovirus.—Rhinoviruses, responsible for more than half of the mild upper respiratory tract infections referred to as "common colds," consist of over 100 different serotypes. This antigenic diversity has prevented the development of successful rhinovirus vaccines. The efficacy of prophylactic short-term interferon alfa has been demonstrated, although its side effects, such as nasal irritation, militate against long-term prophylaxis.⁷²

Approaches to treatment of the "cold" have not yet been successful. Interferons have not proved useful for the treatment of rhinovirus infections. Recombinant DNA technology has provided several novel approaches to the problem of the antigenic diversity of rhinoviruses. Monoclonal antibodies to prevent rhinovirus attachment have been developed,⁷³ and the use of a compound, disoxaril, that interferes with viral uncoating following penetration of the cell membrane has been reported.⁷⁴ Basic biologic processes are now better understood thanks to these new virus-specific inhibitors, making a true prevention and treatment for the common cold more feasible.

Measles

Measles remains a serious health problem in many parts of the world. Recent outbreaks have occurred in the United States despite very high immunization rates. Vaccine failures in young adults, particularly those immunized prior to 1967, may result in severe disease. A safe and effective therapeutic agent against measles could be used to treat the increasing number of immunocompromised children not effectively protected by immunization, young infants who are unable to be immunized, and older children who have not been immunized. At this time, ribavirin is one of the few antiviral compounds that inhibits measles virus replication *in vitro*.⁷⁵ Unfortunately, adequate clinical studies have not yet been performed. Several small, placebo-controlled trials of oral ribavirin, which may have been erratically absorbed, have suggested but not proved efficacy.⁷⁶ Conclusive proof of the utility of ribavirin therapy for measles infections awaits further controlled clinical studies.

Human Papillomaviruses

Papillomaviruses are important causes of benign and malignant tumors in both immunocompetent and immunocompromised hosts. Although we are now convinced that warts come from papillomaviruses instead of toads, we know surprisingly little about the life cycle of this novel class of DNA viruses that consists of at least 60 types.

Juvenile Papillomatosis.—This potentially life-threatening disease ap-

Table 3.—Antiretroviral Drugs Currently in Clinical Trials*

Generic Name	Tradename	Class of Compound	Proposed Mechanism of Action	Formulations	Major Toxicity
AL721	AL721	Lipids	Inhibits viral attachment	Oral	Diarrhea
CD4	Not assigned	Polypeptide	Blocks CD4 receptor for HIV	IM	Not known
Dextran sulfate	Uendex	Sulfonated carbohydrate	Inhibits viral attachment	Oral	Gastrointestinal irritation
Dideoxyinosine	Not assigned	Purine nucleoside	Inhibits reverse transcriptase	Oral	Peripheral neuropathy
Dideoxycytidine	HIVCID	Pyrimidine nucleoside	Inhibits reverse transcriptase	Oral	Peripheral neuropathy
Ribavirin	Virazole	Purine nucleoside	Inhibitor of RNA processing, transcription	Oral, IV	Anemia
Trisodium phosphonoformate	Foscarnet	Pyrophosphate	Inhibits reverse transcriptase	IV	Renal
Zidovudine	Retrovir	Pyrimidine nucleoside	Inhibits reverse transcriptase	Oral	Bone marrow suppression

*The only compound presently Food and Drug Administration approved is zidovudine. HIV indicates human immunodeficiency virus; IM, intramuscular; and IV, intravenous.

pears to be vertically transmitted from a mother with genital warts. Surgery is the only viable management option at present. Specific antiviral drugs are urgently needed to combat this entity. A recent article indicated that recombinant interferon alfa was of no value in the long-term management of respiratory (juvenile) papillomatosis.⁷⁷

Warts.—The most common manifestation of human papillomavirus infections are plantar or hand warts. The preferred therapy is to destroy or remove viral-infected tissue by sonication, freezing, or surgery. Although experimental therapy with topical or intralesional interferon has been attempted for condyloma acuminatum, a sexually transmitted papillomavirus infection, lasting responses to therapy have not been demonstrated.⁷⁸

Hepatitis

Of the three major forms of hepatitis—hepatitis A, hepatitis B, and non-A non-B hepatitis—only hepatitis B has been a target for antiviral therapies. Single-agent chemotherapy using vidarabine, its soluble monophosphate derivative vidarabine monophosphate, and acyclovir have had little effect on chronic hepatitis B.⁷⁹ Combinations of interferon alfa with vidarabine monophosphate have been neurotoxic and without clinical benefit.⁸⁰ A recent promising treatment approach was the combination of corticosteroids followed

by recombinant human interferon alfa.⁸¹ Although only 18 patients were in the treatment arm of this study, 5 (22%) became hepatitis B surface antigen-negative, and 4 of the 5 lost detectable hepatitis B core antigen in their hepatocytes and developed antibody to hepatitis B surface antigen. A large multicenter trial of this treatment regimen is currently under way.

Exotic Diseases

Lassa fever, an endemic viral disease carried by rodents in western Africa, is responsible for approximately 5000 deaths annually. Investigators demonstrated a significant reduction in the case-fatality rate when oral or intravenous ribavirin therapy was initiated within 6 days after onset of fever.⁸²

In addition to the study with Lassa fever, ribavirin has been shown in vitro to inhibit the replication of Hantaan virus, a Bunyamwera virus responsible for Korean hemorrhagic fever.⁸³ The Hantaan virus study could be pertinent to the United States because California encephalitis, our most common form of arboviral encephalitis, is also caused by a Bunyamwera virus.

Human Immunodeficiency Virus (HIV) Infections

A nationwide effort under the aegis of the National Institute of Allergy and Infectious Diseases and the National Cancer Institute, Bethesda, Md, is un-

der way to develop and test candidate drugs against the HIV, the cause of AIDS. A network of 45 AIDS Clinical Trials Units has been established and includes 11 pediatric units. The entire program is called the AIDS Clinical Trials Group.

At the present time, the most promising drug for the treatment of AIDS is zidovudine, which inhibits the reverse transcription of HIV RNA to DNA (Table 3). Zidovudine has been shown to ameliorate, at least temporarily, the neurologic abnormalities associated with pediatric AIDS.⁸⁴ Zidovudine is being intensively studied under pediatric protocols conducted by the AIDS Clinical Trials Group, which include its use in combination with immunoglobulin and a placebo-controlled study in HIV-infected children with minimal symptoms. An exciting concept that is currently being evaluated by the AIDS Clinical Trials Group is the administration of zidovudine to pregnant, HIV-infected women between the 26th and 38th week of gestation or to 1-day-old neonates in an attempt to prevent perinatal acquisition of the virus. Unfortunately, virologists have not yet determined the best test to gauge the antiviral effect of zidovudine. The dilemma is that peripheral blood mononuclear cell cultures often remain culture-positive for HIV during therapy, and decreases in serum p24 antigen levels (a test used to detect amounts of HIV protein) can be documented in only

some cases because the majority of HIV-infected patients have undetectable serum levels of p24 antigen when therapy is started. Potential problems with zidovudine include bone marrow toxicity that can be dose-limiting, and the emergence of resistant HIV strains during therapy.⁸⁵ This recurring specter of viral resistance to antiviral drugs has spurred the development of rapid antiviral sensitivity assays, such as described by Swierkosz et al.⁸⁶

Children represent a minority of the HIV-infected patients in the United States. Therefore, pediatric treatment protocols have lagged behind studies designed for adults. A number of drugs are now being tested in children, including dideoxycytidine, dideoxyinosine, ribavirin, and soluble CD4 (Table 3). An important strategy being investigated in adults would definitely be applicable to children. That strategy is to treat asymptomatic patients with antiviral drugs before severe immune dysfunction develops in order to lengthen the time from infection to expression of HIV disease. We encourage physicians caring for HIV-infected children to contact the nearest AIDS Clinical Trials Unit or the National Institute of Allergy and Infectious Diseases AIDS Clinical

Trials Information Service (1-800-TRI-ALS-A) for details about available trials, including the doses used in these protocols.

THE FUTURE

Two major events have accelerated progress in antiviral chemotherapy. The first was the development of acyclovir. The 1988 Nobel Prize in medicine was shared by three investigators. Two of them, Gertrude Elion and George Hitchings, attained the Nobel Prize in part because of their research on acyclovir. The success of acyclovir has accelerated collaborative efforts in antiviral research between universities and the pharmaceutical industry. Before acyclovir, antiviral drugs were considered by most potential industrial sponsors to be too risky to warrant the expense required to develop them.

The other event, of course, is the global tragedy of AIDS. A desperate need to develop AIDS treatments is producing a proliferation of antiviral compounds. Nearly every step in the unique replicative cycle of HIV has been targeted for antiviral attack. Drugs that inhibit a specific stage of viral replication — reverse transcription — are presently the focus of attention, but

future agents are being designed to block even earlier stages of viral infection, such as attachment, penetration, and uncoating. Soluble CD4, for example, is a promising polypeptide that could prevent attachment of HIV to the cell, or halt cell-to-cell transfer of the virus.⁸⁷ Utilizing the tools of molecular virology and genetic engineering, virologists are designing an increasing array of compounds that interfere with viral regulatory genes, downregulate viral production, or cause structural genes to synthesize defective, noninfectious viral particles. The most promising drugs that pass safely through preclinical screening will be funneled into the national testing network. We believe that the experience being amassed in these national collaborative AIDS clinical trials will not only be relevant to AIDS, but will also serve as an invaluable resource for the development of antiviral treatment strategies against many of the common viral diseases of children.

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Injuries Among 4- to 9-Year-Old Restrained Motor Vehicle Occupants by Seat Location and Crash Impact Site

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• Four- to 9-year-old children are a special group with respect to motor vehicle occupant restraints. Having outgrown child safety seats, they are often placed in adult seat belts. This study was undertaken to examine patterns of injury among restrained 4- to 9-year-olds by seat location and crash impact site. The data were obtained from an ongoing hospital-based monitoring system. Seventy percent of the sample sustained a head or face injury. Upper-torso and extremity injuries were infrequent. Lower torso injuries occurred primarily in frontal impacts in both the back and front seats. Frontal impacts resulted in a greater proportion of serious injuries than rear impacts. The most serious injuries, however, occurred to children seated on the side of impact in lateral collisions. Questions must be raised regarding the appropriateness of the present restraint system for young children. Recommendations, given current seat belt systems, are provided. However, technological improvements in vehicle design and belt systems are needed to improve protection, particularly in lateral impacts.

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A marked increase in restraint use among motor vehicle occupants of all ages, including children, has occurred as a result of mandatory restraint use laws and education regarding the protective effects of seat belts and child safety seats. The effectiveness

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of restraint legislation as well as the effectiveness of seat belts and child safety seats in reducing fatalities and injuries has been documented.¹⁻⁴ As restraint use increases, many restrained occupants escape injury in vehicle crashes. However, the increase in restraint use may also result in an increase

in the number of restrained occupants involved in crashes who come to the emergency department for evaluation and treatment of injuries.

Vehicle restraints that protect from injury also change the pattern and severity of injuries. Rutherford et al⁵ and others,⁶⁻⁸ for example, have reported an increase in neck injuries with increased seat belt use. Intra-abdominal injuries as well as lumbar spine injuries have also been reported in vehicle crashes as a result of hyperflexion and compression of the abdomen between the lap belt and the lumbar spine.^{10,11}

Previous research has indicated different mechanisms and patterns of injury among restrained children by age.⁹ In the pediatric population, 4- to 9-year-old children are a special group with respect to motor vehicle occupant restraint. These children have outgrown the child safety seats specially designed for younger children. They are placed in seat belt systems designed for the adult body configuration. Specific anatomic and anthropometric features are relevant to seat belt use for children in this age group. The overall weight and length characteristics of children are markedly different from those of adults. The child's sitting height is less than that of the average adult, and the center of gravity, which varies with age, length, and weight, is located on the torso above the level of the lap belt. These features alter the fit of the restraint system. The greater proportion of body mass above the belt may cause more forward motion, with an increased risk of head impact with interior parts of the vehicle. Jackknifing over the lap belt can occur in a lap belt restraint system. With lap/shoulder belts, the shoulder portion may lie over the face and neck of the young child. Another anatomic concern relates to the anchor point for the lap portion of the belt system. The lap belt is designed to restrain the body just below its center of gravity at a horizontal plane through the antero-

superior iliac crest of a standing adult. The anterior iliac crests of a child are smaller than those of an adult and are not fully developed to serve as anchor points for a seat belt until the child is approximately 10 years of age. Therefore, the belt may ride up over the abdomen of the young child. Related to this is the fact that the intra-abdominal organs of young children are less protected by the bony pelvis and thoracic cage compared with adults.¹² The tilt of the child's pelvis and the maintenance of upright posture also influence the fit of the seat belt. In addition to these physical features, the behavioral characteristics of young children may influence the protective effects of seat belts, eg, the child may readjust his or her seating position, lean forward and move about, or engage in activities that alter the proper "fit" of the belt system.

This study was designed to examine patterns and severity of injury among restrained 4- to 9-year-old children by seat location and crash impact site. The intent of this study was to analyze injuries of restrained children, not to compare restrained and unrestrained children.

METHODS

Data were obtained from a larger, ongoing hospital-based monitoring system for pediatric motor vehicle occupant trauma. The system has been in operation since 1981 and consists of nine hospital emergency departments and the coroner's office in a single urban county with a population of approximately 2 million. Hospitals for this system were selected on the basis of geographic location and annual number of emergency department visits. Four of the five designated trauma centers were included.

Data were collected on all children through the age of 14 years who came to the emergency department for evaluation and treatment of injuries after involvement in a motor vehicle crash. The parent or guardian completed a questionnaire at the time of the emergency department visit or through a follow-up telephone interview. Questions included age of

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Table 1.—Severity of Injuries in Restrained 4- to 9-Year-Olds by Seat Location and Impact Site

Group	Seat Location	Impact Site	No. of Children	No. (%) by Maximum Abbreviated Injury Score				Mean	P*
				1	2	≥3			
1	Front or back outboard	Lateral (off site)	18	18 (100)	0	0		1.0	.005
		Lateral (on site)	27	16 (59)	7 (26)	4 (15)		1.6	
2	Back outboard	Frontal	21	19 (90)	2 (10)	0		1.1	NS
		Rear	27	25 (93)	0	2 (7)		1.15	
3	Front passenger	Frontal	26	21 (81)	2 (8)	3 (12)		1.38	NS
		Rear	12	12 (100)	0	0		1.0	
Total	131	110 (84)	11 (8)	10 (8)	

*NS indicates not significant.

the child, seat location, restraint use, how the child was injured, type of crash, and crash impact site(s). Data on injuries, treatment, final diagnosis, and disposition from the emergency department were provided by emergency department medical staff or were abstracted from the medical records.

Information on restraint use was initially obtained through parent report. In the course of the interview the parent was asked the following question: "At the time of the accident was your child: sitting alone, standing alone, in the arms or lap of another passenger, lying down, wearing a seat belt (lap or lap/shoulder belt), in a child safety seat, or other?" This question was embedded within a series of questions regarding the child and the crash to decrease the chance of biasing responses in favor of restraint use. For those who indicated that the child was restrained, additional questions were asked regarding how the child was injured and what happened to the child and the restraint system during the crash. All of these cases were reviewed by the research team using hospital records and available newspaper and police reports. Cases in which the research team doubted whether the child was restrained were coded as such and were removed from this analysis.

Three injury measures were used. Specific injuries sustained by each child were coded. Severity of injury was coded using the Abbreviated Injury Scale (AIS-85).¹³ The AIS is scored as follows: AIS=1, minor; AIS=2, moderate; AIS=3, serious; AIS=4, severe; AIS=5, critical; and AIS=6, untreatable. Utilizing the AIS scoring method, a Maximum Abbreviated Injury Score (MAIS) that represents overall injury severity was assigned to each case. For children with multiple injuries, the MAIS is the single highest AIS code; for children with only one injury the AIS is also the MAIS. Injuries were also assigned to the following anatomic sites: head and face, upper torso, lower torso, upper extremity, lower extremity, and spine, and the highest AIS for each anatomic site was determined.

The sample consisted of children 4 through 9 years of age who were seen in monitored emergency departments or the coroner's office after involvement in a motor vehicle crash between 1981 and 1987. Only restrained children who were involved in a crash between two passenger vehicles with a single impact site were included in the analysis. Multiple vehicle crashes, rollovers, crashes involving trucks and other nonpassenger vehicles, and crashes with objects were excluded from the analysis. The analysis also excluded cases in which there was more than one crash impact site. The analysis was confined to the three most common passenger seating positions (front passenger, back passenger, and back of driver [back outboard seats]) and three types of impacts (lateral, frontal, and rear). There were 131 cases of 4- to 9-year-old restrained children seated in these seat locations who were injured in the three types of vehicle-to-vehicle crashes.

The cases were placed into one of three groups based on impact site. Group 1 cases included children in all three seat locations who were involved in lateral impact collisions. A comparison was made between on-site (impact on the side where the child was seated) and off-site (impact on the side opposite the child) lateral impacts. Group 2 cases included children in the back seat involved in frontal or rear impacts. Those in the back middle seat were eliminated because of small numbers and differences in the kinematics of occupant movement and occupant contact areas in this position compared with the outboard positions. Group 3 cases included children in the front passenger seat involved in frontal or rear impacts.

Group	Seat Position	Impact Site Comparison
1	Front passenger and back outboard	Lateral (on site vs off site)
2	Back outboard	Frontal vs rear
3	Front passenger	Frontal vs rear

Analysis consisted of comparisons of overall injury severity scores (MAIS). The anatomic site of injury within each group for the various impact sites was also compared using χ^2 analysis. The analysis of variance statistical test was used to compare overall injury severity and severity of head and face injuries for the various impact sites. Small numbers and primarily minor injuries prevented analysis of the variance in injury severity to other body areas. $P \leq .05$ was considered statistically significant.

RESULTS

Injury Severity

Table 1 shows the distribution of MAIS by seat location and impact site. Among those in group 1 (lateral impact), all the serious injuries were incurred in on-site impacts. Forty-one percent of those in on-site lateral impacts sustained injuries with an MAIS of 2 or greater, far exceeding the proportion of serious injuries in any other group. None of those involved in off-site lateral impacts sustained more than a minor injury (MAIS=1). Among those in group 2 (the back outboard seats), 10% sustained an injury with an MAIS of 2 or greater in frontal impacts compared with 7% in rear impacts. In group 3 (the front passenger seat), all of the serious injuries were in frontal impacts; 20% of these children sustained an injury with an MAIS of 2 or greater. Of those in group 3 in rear impacts, none received more than a minor injury (MAIS=1), similar to the results seen in off-site lateral impacts. Significant differences in injury severity, however, were only found in group 1. The mean MAIS for on-site lateral impacts was 1.6, compared with 1.0 for off-site impacts ($P = .005$).

Anatomic Site of Injury

Head and Face Injuries.—Seventy percent of the children sustained an injury to the head or face. Although there were no significant differences in the percentage who sustained head and face injuries within each group, trends were apparent. The largest proportions were in frontal impacts in both the back (81%) and front (77%) seats. Head and face injuries were somewhat less frequent among those in rear impacts, although a greater percentage was seen among those in the back seat (67%) compared with the front seat (50%). The only significant difference in the severity of head and face injuries was found in

Table 2.—Head and Face Injuries in Restrained 4- to 9-Year-Olds by Seat Location and Impact Site

Group	Seat Location	Impact Site	No. of Children	Head or Face Injury, No. (%)	P*	Mean Abbreviated Injury Score of Children With Head or Face Injury	P*
1	Front or back outboard	Lateral (off site)	18	12 (67)	NS	1.0	.03
		Lateral (on site)	27	19 (70)		1.5	
2	Back outboard	Frontal	21	17 (81)	NS	1.2	NS
		Rear	27	18 (67)		1.1	
3	Front passenger	Frontal	26	20 (77)	NS	1.2	NS
		Rear	12	6 (50)		1.0	
Total	131	92 (70)	...	1.2	...

*NS indicates not significant.

Table 3.—Lower-Torso Injuries in Restrained 4- to 9-Year-Olds by Seat Location and Impact Site

Group	Seat Location	Impact Site	No. of Children	Lower-Torso Injury, No. (%)	P*
1	Front or back outboard	Lateral (off site)	18	4 (22)	NS
		Lateral (on site)	27	6 (22)	
2	Back outboard	Frontal	21	6 (29)	.01
		Rear	27	1 (4)	
3	Front passenger	Frontal	26	7 (27)	.05
		Rear	12	0	
Total	131	24 (18)	...

*NS indicates not significant.

Table 4.—Spine Injuries in Restrained 4- to 9-Year-Olds by Seat Location and Impact Site

Group	Seat Location	Impact Site	No. of Children	Spine Injury, No. (%)	P*
1	Front or back outboard	Lateral (off site)	18	3 (17)	NS
		Lateral (on site)	27	2 (7)	
2	Back outboard	Frontal	21	1 (5)	NS
		Rear	27	6 (22)	
3	Front passenger	Frontal	26	3 (12)	.03
		Rear	12	5 (42)	
Total	131	20 (15)	...

*NS indicates not significant.

group 1; on-site lateral impacts resulted in more serious head and face injuries than off-site lateral impacts ($P=.03$, Table 2).

Torso Injuries.—Upper-torso injuries were infrequent, sustained by only 6% of the sample. No significant differences were found between seat location and impact sites, and the injuries were predominantly minor (AIS = 1).

Lower-torso injuries were incurred by 18% of the sample (Table 3). In both the back and front seats (groups 2 and

3), frontal impacts resulted in a significantly greater proportion of lower-torso injuries than did rear impacts. Most of the injuries were minor abrasions or contusions. Two children with serious torso injuries were in the front seat in frontal impacts, and the other was in the back seat in an on-site lateral impact.

Extremity Injuries.—Upper-extremity injuries were incurred by 11% of the sample. Lower-extremity injuries were also sustained by 11% of the sample. There were no significant dif-

ferences in the proportion of extremity injuries by seat location and impact site for either upper or lower extremities. One lower-extremity fracture occurred in a lateral on-site impact, and two occurred in the back seat by contact of the leg with the back of the front seat in rear impact collisions.

Spine Injuries.—Spinal injuries were predominantly rear impact phenomena (Table 4). By far the greatest proportion was seen among those in the front seat (42%), followed by those in the back seat in rear impacts (22%). The injuries were predominantly minor strains. Only one child, 6 years of age, who was in the back seat in a rear impact, sustained a serious spinal injury. This child struck the back of the front seat and sustained a cervical spine subluxation and multiple skull fractures.

Case Descriptions of Seriously Injured Children

Fifteen percent of all children sustained an injury with an MAIS of 2 or greater. Over half of the serious injuries (MAIS ≥ 2) were internal head injuries. Case descriptions are presented in Table 5.

Group 1 (Outboard Position, Lateral Impact).—Among all of the seriously injured restrained children with an MAIS of 2 or greater, the greatest proportion consisted of children in the outboard seating positions involved in on-site lateral impacts. In fact, all of the serious injuries in lateral impacts were to children seated on the side of the impact of the crash. The major injury pattern in these children was either a serious head injury or an extremity injury. This occurred in both the back and front seats in lap as well as lap/shoulder belts. Vehicle intrusion in a number of these cases indicates the severe nature of several of these lateral impacts.

Group 2 (Back Seat, Frontal or Rear Impact).—In this group, serious injuries were equally divided between frontal and rear impacts. The serious injuries were either head injuries primarily caused by hyperextension of the upper torso over the lap belt and impact with the back of the front seat or extremity fractures, also caused by impact with the back of the front seat. No serious abdominal injuries were seen in this group. Only one child sustained a serious spinal injury. This involved a 6-year-old in a rear impact who struck the

Table 5.—Serious Injuries in Restrained 4- to 9-Year-Olds by Seat Location and Impact Site

Patient No./ Age, y	Seat Location	Impact Site	Restraint	Mechanism of Injury	Injuries	Maximum Abbreviated Injury Score
Group 1 (Front or Back Outboard Seat, Lateral Impact)						
1/9	Front passenger	Lateral (on site)	Restrained, presumably lap/shoulder	Intrusion of vehicle, interior impact	R fractured ribs, lung contusion, subarachnoid hemorrhage, R frontal hematoma	4
2/5	Front passenger	Lateral (on site)	Lap/shoulder	Intrusion of vehicle, interior impact	R femur fracture, lip contusion	3
3/9	Front passenger	Lateral (on site)	Lap/shoulder	Intrusion of vehicle, interior impact	Depressed R frontal skull fracture, head laceration, R leg contusion	3
4/7	Front passenger	Lateral (on site)	Lap	Hit windshield	L skull fracture (vault), concussion, L forehead laceration, knee abrasion	2
5/9	Front passenger	Lateral (on site)	Lap/shoulder	Intrusion of vehicle, interior impact	Concussion, R clavicle fracture, R leg contusion	2
6/8	Back passenger	Lateral (on site)	Lap	Unknown	L cerebral contusion, L parietal skull fracture, bladder contusion	3
7/9	Back driver	Lateral (on site)	Lap	Hit door	Concussion, L forehead hematoma	2
8/5	Back driver	Lateral (on site)	Lap	Hit door	L clavicle fracture, L head and hip contusions	2
9/4	Back driver	Lateral (on site)	Lap	Hit door	L clavicle fracture, L head contusion	2
10/7	Back driver	Lateral (on site)	Lap	Flying glass	Head laceration	2
11/7	Back driver	Lateral (on site)	Lap	Hit back of seat	L humerus fracture, L leg abrasion	2
Group 2 (Back Outboard Seat, Frontal or Rear Impact)						
12/5	Back passenger	Rear	Lap	Back seat pushed up against front seat	Bilateral femur fractures, R cheek and L elbow abrasions	3
13/6	Back passenger	Rear	Lap	Hit back of front seat	Depressed fracture of L occipital skull, bilateral comminuted fracture of frontal skull, subluxation of cervical spine	3
14/6	Back passenger	Frontal	Lap	Hit back of front seat and strained against seat belt	Concussion, facial laceration, abdominal contusion	2
Group 3 (Front Passenger Seat, Frontal or Rear Impact)						
15/8	Back driver	Frontal	Lap	Hit back of front seat	Extensive facial laceration	2
16/4	Front passenger	Frontal	Seat belt	Injured from seat belt	Ileal perforation with peritoneal hemorrhage	5
17/9	Front passenger	Frontal	Lap/shoulder	Hit windshield	Depressed occipital skull fracture, concussion, facial laceration	3
18/8	Front passenger	Frontal	Lap/shoulder	Hit dashboard and windshield	Cerebral edema, small contusion on forehead	3
19/7	Front passenger	Frontal	Lap/shoulder with shoulder portion behind	Hit dashboard and strained against seat belt	Concussion, abdominal contusions, forehead abrasions	2
20/9	Front passenger	Frontal	Lap/shoulder with shoulder portion behind and belt not securely fastened	Came out of seat belt and hit windshield and dashboard, striking abdomen and face	Liver laceration, facial abrasions	2

back of the front seat and sustained multiple skull fractures and subluxation of the cervical spine.

Group 3 (Front Seat, Frontal or Rear Impact).—All of the serious injuries to this group of children in the front

seat involved in frontal impacts. One child sustained an ileal perforation caused by the seat belt. All of the other seriously injured children struck the front of the vehicle. In two cases the shoulder part of the belt was not proper-

ly used; the shoulder portion of the belt was flipped behind the child. One child sustained a liver laceration, the other, a serious head injury. In the other two cases, even though the children were using the shoulder portion of the seat

belt, they were still moved forward and hit the windshield or dashboard, sustaining serious head injuries.

COMMENT

This study was undertaken to examine injuries sustained by children 4 to 9 years of age who were restrained at the time of a motor vehicle crash. This age group was selected because it is a special group with respect to occupant protection. These children have outgrown the child safety seat and are placed in a seat belt system designed for the adult body configuration. Patterns and severity of injury were analyzed by seat location and crash impact site. In the back seat these children were restrained in lap belts, and in the front seat they were in lap/shoulder belts.

One of the most striking features of the analysis was that among these restrained 4- to 9-year-olds there was a substantial proportion of head and face injuries; 70% of the entire sample sustained an injury to the face or head. This occurred in all seat locations and impact sites but was more of a problem in frontal impacts in both the front and back seats. Most of the head and face injuries were minor; however, 12% were serious and included injuries such as concussions, skull fractures, and internal head injuries. Several of these children struck the windshield or dashboard if they were in the front seat or the back of the front seat if they were in the back seat. A significant proportion of the most severe head injuries was sustained by children involved in on-site lateral impacts.

Another important finding was the marked proportion of serious injuries sustained by restrained children in on-site lateral impacts; 41% of these children had injuries with an MAIS of 2 or greater. The injuries primarily occurred as a result of vehicle deformation into the passenger compartment in the area where the child was seated. Thus, in the case of a serious lateral impact crash with vehicle deformation, belt systems do not appear to provide adequate protection.

A recent National Transportation Safety Board study reported a substantial number of abdominal injuries among those involved in frontal collisions who were restrained in lap belts in the rear seat.¹⁴ We did not see this in this study.

We had only two cases of serious injuries to rear-seated children in frontal impacts over the 7 years, and neither child sustained a serious internal abdominal injury. One child sustained a concussion and the other an extensive facial laceration. The serious spinal injury in this study was sustained by a child lap-belted in the back seat in a rear impact.

It is clear from this study that occupant protection in the lateral on-site impact requires changes in car design, eg, thickened doors and better padding to absorb more energy of the impact and increased space between the door and the occupant. Based on the data in this study and until improvements in vehicle design have been made, the middle rear seat may be the safest in the event of lateral impacts.

Except for on-site lateral impacts, most of the injuries to seat-belted children were minor. The seat belt-induced injuries were few and survivable. Since no children were ejected from the vehicle, it appears that seat belts prevented ejection. However, in view of the fact that a large proportion of the restrained children sustained injury to the head and face, there is a need for research to determine the fit of vehicle seat belts for children of this age. Child-sized dummies of various sizes should be developed and tested with all types of restraint systems. In addition, data on children in real-life crashes must continue to be gathered. Based on the findings of dummy crash testing and real-life crashes, seat belts may need to be modified or special seats may need to be designed to provide optimal occupant protection for children in the 4- to 9-year age group who have outgrown child safety seats.

While transitional restraint systems, ie, booster seats, are available for 4- to 9-year-old children, observational studies indicate low usage rates. At this point, crash data on young children in booster seats are not available. Additional research on the effectiveness of boosters in real-life crashes is needed. If the current booster seats are indeed protective, measures to increase usage should be addressed. Alternatively, if seat belts and current booster seats do not fit or optimally protect children who have outgrown child safety seats, it may be necessary to design a seat for the 4- to

9-year-old child similar to child safety seats.

Until a more protective system is developed and is in widespread use, children 4 to 9 years of age should use available vehicle seat belts. For children in the front seat, moving the seat as far back from the dashboard as possible, and for those in the back seat, moving the front seat forward, may eliminate some of the interior impact injuries. Use of lap/shoulder belts in the rear seat may also help to eliminate some of the more forceful head impacts. Overall, seat belts work, and parents must require children to use them.

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Long-term Outcome of Adolescents With Anorexia Nervosa

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• The long-term outcome of 49 adolescent girls hospitalized for the treatment of anorexia nervosa on a pediatric service was determined by personal interview an average of 80 ± 21 months after admission to the hospital. The mean age at follow-up was 22.7 years. Between admission to the hospital and follow-up, body weight increased, on average, from 72.1% to 96.1% of ideal. Amenorrhea occurred in all subjects, but menstruation began or resumed in 80% of patients after hospitalization, at a mean body weight $90.3\% \pm 6.5\%$ of ideal. A total of 15 pregnancies resulted in 2 elective abortions, 3 ongoing pregnancies, and 10 healthy newborns. No subject who desired to become pregnant was unable to conceive. Almost half of the subjects (22 of 45) acquired binge eating patterns after hospitalization. Overall, 86% had a satisfactory outcome. These data indicated that adolescents with anorexia nervosa can be successfully treated with a developmentally oriented, multidisciplinary approach that includes inpatient and outpatient management based in pediatrics.

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Anorexia nervosa is an eating disorder characterized by voluntary starvation due to a disturbed body image in which one's body is perceived as being fat (even at normal or low weight), an intense fear of obesity, and a relentless obsession to become thinner.¹ Occurring almost exclusively in adolescent girls, it results in numerous physiologic sequelae, including extreme weight loss and malnutrition, marked hypometabolism, amenorrhea, and osteoporosis.² Mortality as high as 50% has been re-

ported, but recent reports suggest a death rate between 2% and 8%.³ Although mortality has decreased, the incidence has increased during the last few decades to "near epidemic" levels.⁴ Recent studies of anorexia nervosa among middle-class adolescent girls report a prevalence rate of between 1% and 4%.⁵ Because underlying psychological and developmental factors play a significant etiologic role, multidisciplinary treatment including medical care, behavior modification, and psychotherapy is most successful.⁶ However, because psychosocial factors often dominate the clinical presentation, the pediatrician's role in treatment often is relegated to providing medical backup rather than patient management.⁷

Since the course of the illness is protracted, determination of outcome of treatment can be made only on long-term follow-up. Morgan and colleagues⁸ advise that the follow-up interval should be at least 4 years. Most studies fulfilling this criterion among child and adolescent populations are reported in the psychiatric literature, with little attention paid to biologic outcome.⁹ Outcome studies in the pediatric literature generally have been short term.¹⁰

We report the long-term outcome of 49 girls admitted consecutively to our hospital on the pediatric service for the treatment of anorexia nervosa. All but eight patients were cared for by the same pediatrician (R.E.K.). Data on mortality, morbidity, weight, eating and purging behaviors (including crossover to binge eating), and psychosocial functioning were obtained. We also determined fertility history and the weight at which menstrual periods resumed. Specifically, we sought to describe the long-range prognosis for adolescents with anorexia nervosa whose care was managed primarily by pediatricians in a multidisciplinary health care team.

PATIENTS AND METHODS

The medical records of all girls who were admitted to Strong Memorial Hospital (Rochester, NY) during the 6-year interval between January 1, 1979, and December 31, 1984, for at least 2 weeks of treatment for anorexia nervosa ($N=62$) by a pediatrician with special interest in adolescent medicine were reviewed. Seven subjects discharged from the hospital with a diagnosis of anorexia nervosa, but who fulfilled criteria for bulimia nervosa only, were eliminated from further consideration. The remaining 55 subjects, all white adolescents who met criteria for the diagnosis of anorexia nervosa, were contacted by mail and telephone to be included in this long-term outcome study. One subject had committed suicide, 2 refused to participate, two gave limited information, and 1 could not be located. The remaining 49 subjects (89% response rate) form the study sample.

Structured personal interviews were held with 47 subjects; parents alone provided information for 2 subjects. Four patients did not complete the entire interview, resulting in a denominator of 45 for some variables. To minimize potential bias regarding the assessment of outcome, each interview was conducted by a medical student (B.H.C.) who had previously reviewed each subject's medical record to obtain information about hospitalization, but who had had no previous contact with any subject.

The inpatient treatment program for these patients has been previously described.¹¹ All subjects received medical treatment focused on physical health and weight gain, proper nutrition, normal adolescent development, and some psychotherapy (individual, family, group, either alone or in combination) before, during, and after hospitalization. Specifically, 14 (29%) had received individual therapy only, and 2 (4%) had received family therapy only. Five subjects (10%) had received both individual and group therapy, while 14 (29%) had received both individual and family therapy. An additional 14 (29%) had received a combination of individual, group, and family therapy. At follow-up, 6 (12%) were still receiving medical treatment, 6 (12%) were in psychotherapy, but only 3 (6%) were still obtaining both medical and psychological

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Table 1.—Demographic Variables for 49 Adolescents Hospitalized for Treatment of Anorexia Nervosa	
Variable	Value
At first hospitalization, mean (range)	
Age, y	16.0 (9-22)
% of ideal body weight (IBW) for sex, height, and age	72.1 (47-88)
At follow-up	
Age, y, mean (range)	22.7 (14-29)
% of IBW, mean (range)	96.1 (72-137)
No. (%) of patients by % of IBW	
70%-89%	17 (35)
90%-109%	26 (53)
≥110%	6 (12)
Time since first admission, mo, mean (range)	79.8 (48-150)

care for their anorexia nervosa. Although most patients received formal mental health care, we emphasize that the overall management of care of these patients was provided by pediatricians in pediatric settings.

Interview data were used to determine a score on the Global Assessment Scale (GAS) for each subject.¹² This instrument rates subjects with eating disorders in five clinically relevant areas (percentage of ideal body weight [IBW] for sex, height, and age; menstrual history; eating habits; social adjustment; and education/employment) and provides a single outcome score. By convention, scores are divided into four outcome categories: 0 to 3, excellent; 4 to 7, much improved; 8 to 11, symptomatic; and 12 to 23, poor. A score of less than 8 indicates a satisfactory outcome. Data were analyzed and tests of statistical significance were performed with the SAS computer program, release 5.18. Tables 1 and 2 show pertinent weight and demographic variables for this sample.

RESULTS

Mortality

One patient was known to have committed suicide, and 1 patient could not be contacted. Therefore, the highest possible mortality among the original 55 subjects was less than 4%. The patient who committed suicide had developed major depression requiring psychiatric care, had attempted suicide previously, and had developed intractable bulimia nervosa. Two other patients included in the study had attempted suicide.

Morbidity

The most commonly reported physical symptoms were related to the gastrointestinal tract. Eight subjects com-

Table 2.—Education, Employment, and Living Arrangements at Follow-up			
	No. (%) of Patients by Age, y		
	<19 (n=8)	19-21 (n=12)	≥22 (n=29)
Enrolled in school	8 (100)	8 (67)	8 (28)
Employed outside the home	6 (75)	10 (83)	23 (79)
Living with parents	8 (100)	7 (58)	5 (17)
Living with friends	0 (0)	3 (25)	8 (28)
Living alone	0 (0)	1 (8)	4 (14)
Living with spouse	0 (0)	1 (8)	12 (41)

plained of chronic constipation, even among those who had attained normal weight. Irritable bowel syndrome was reported by two subjects, and two others had had a perforated duodenal ulcer.

One subject who had vomited for more than 7 years reported frequent involuntary reflux of stomach contents. Significant dental enamel erosion occurred in two subjects who had been vomiting for an average of 10.5 years.

One of the youngest subjects was being studied for short stature and primary amenorrhea. One individual had developed hypothyroidism. The remaining 32 subjects had enjoyed relatively good health, except for some problems during pregnancy (see next section). More than half (59%) of patients reported no health problems after discharge from the hospital.

The majority of subjects (36 [73%]) were not taking any medication regularly. The most common prescription medicine, being taken by 5 subjects, was oral contraceptive pills. Four subjects (8%) were taking psychoactive medications: 2 were taking imipramine, 1 was taking lithium carbonate, and 1 was taking both lithium carbonate and phenelzine sulfate (a monoamine oxidase inhibitor). Three were taking bulk-forming laxatives because of persistent constipation. In general, the group was relatively healthy and did not complain of persistent medical problems.

Weight, Menstruation, and Fertility

Although the lowest weight reached by the group (\pm SD) averaged only $72.1\% \pm 9.2\%$ of IBW, at follow-up their weight had increased significantly ($t=12.2$; $P<.01$), having attained a mean of $96.1\% \pm 13.3\%$ of IBW. Seventeen individuals (35%) weighed less than 90% of their IBW, 6 individuals

(12%) were more than 110% of their IBW, and 26 (53%) were between 90% and 110% of their IBW.

All subjects experienced amenorrhea during their illness. Eleven subjects developed anorexia nervosa before menarche; the remaining 38 individuals had secondary amenorrhea. Amenorrhea persisted at follow-up in 10 subjects. Three subjects, aged 15, 18, and 19 years, had primary amenorrhea and had developed their eating disorder at the ages of 9, 12, and 12 years, respectively. One of the 10 amenorrheic subjects had resumed her menses after hospitalization but had not menstruated in the 6 months before follow-up. The present mean percentage of IBW of the amenorrheic group was $84.6\% \pm 7.1\%$ of IBW (range, 72% to 90%; Table 3).

In contrast to the amenorrheic group, the 38 individuals who were menstruating at follow-up weighed significantly more, averaging $98.9\% \pm 12.7\%$ of IBW ($t=3.4$; $P<.01$). Those who were menstruating regularly weighed essentially the same as those who had irregular or sporadic menses. One subject had regular menses at 94% of her IBW but had been cycled with hormonal replacement when she was at only 82% of her IBW; the other four subjects taking oral contraceptives had started taking them after their periods had resumed spontaneously.

Overall, 39 (80%) of 49 subjects had gained sufficient weight at some time after hospitalization either to initiate or to regain menstruation. Eight of 11 patients who had primary amenorrhea eventually began to menstruate. Their average age at menarche was obviously delayed, averaging 16.3 years. Although 31 (82%) of 38 subjects with secondary amenorrhea eventually resumed menstruation, the interval from

Table 3.—Menstruation, Weight on Return of Menstruation, and Fertility After Treatment for Anorexia Nervosa

Variable	Value
No menses in previous 6 mo	
No. (%) of patients	10 (21)
% of ideal body weight (IBW), mean (range)	85 (72-93)
Menses in previous 6 mo	
No. (%) of patients	38 (79)
% of IBW, mean (range)	98 (81-137)
Regular*	
No. of patients	32
% of IBW, mean (range)	99 (81-137)
Sporadic or irregular	
No. of patients	6
% of IBW, mean (range)	96 (86-117)
Mean % of IBW on return of menses†	90.3 ± 6.5
Primary amenorrhea	91.6 ± 9.6
Secondary amenorrhea	89.9 ± 5.5
No. of pregnancies	15 (9 patients)
Deliveries	10
Abortions	2
Ongoing	3
Difficulty becoming pregnant	0

*Includes two pregnant subjects whose weight is not included in the determination of mean percentage of IBW.

†Two subjects (one who began menses because of hormonal replacement and another whose return of menses was delayed by the occurrence of hypothyroidism until the patient reached 72 kg) are not included in the determination of the mean percentage of IBW.

the cessation to the return of menses varied widely, from a few months to more than 6 years. The reported weight at which menses returned averaged $90.3\% \pm 6.5\%$ of IBW, with a range of 79% to 101% of IBW. There was not a significant difference in the percentage of IBW on return of menses for those who were menstruating sporadically compared with those who were menstruating regularly (92.8% vs 89.5% of IBW).

Thirteen subjects were married; 8 of them had become pregnant. These women had experienced 14 pregnancies and 10 deliveries since the onset of their anorexia nervosa. Three were pregnant at the time of follow-up, and another had had an induced abortion. One of the unmarried subjects also had had an induced abortion, bringing to 15 the total number of known pregnancies in the sample. No miscarriages were reported. There were 2 complicated pregnancies, both occurring in the same indi-

Table 4.—Food-Related Habits Before and After Treatment Started and at Follow-up (N = 45)

Habit	No. (%)		
	Before Treatment Started	After Treatment Started	At Follow-up
Daily food restriction	45 (100)	...	12 (27)
No food restriction	0 (0)	...	20 (44)
Exercise	33 (73)	2 (4)	17 (38)
Binge eating	6 (13)	22 (49)	13 (29)
Vomiting	11 (24)	12 (27)	10 (22)
Ipecac	2 (4)	4 (9)	1 (2)
Laxatives	11 (24)	12 (27)	4 (9)
Diet pills	10 (22)	7 (16)	1 (2)
Diuretics	0 (0)	4 (9)	1 (2)

vidual; toxemia occurred in the first and gestational diabetes in the second pregnancy. All 10 offspring of the 7 subjects who had given birth had uncomplicated neonatal courses.

No one reported infertility. All of those who desired to become pregnant had been able to do so within 1 year. One of the three pregnant subjects had been taking birth control pills until 8 months before data collection. She became pregnant 4 months after the interview.

In summary, 80% of patients regained their menstrual periods when their weight rose to within 10% of ideal. No one desiring pregnancy was unable to conceive. When subjects did conceive, there was no evidence of adverse neonatal outcome.

Food-Related Habits

Detailed histories about eating and weight loss methods obtained from 45 subjects are summarized in Table 4. All subjects, by definition, had engaged in daily food restriction before treatment began. At the time of follow-up, 44% of subjects reported no regular dieting behavior, while 27% reported daily food restriction and 29% limited their intake, but not on a daily basis. Compulsive exercise was a commonly used means of weight control, employed by 73% of subjects before treatment started. At follow-up 38% still exercised regularly to control their weight.

Purging (vomiting or laxative use) as a means to lose weight was used at some time in the course of the illness by more than half of the subjects (23 of 45). Ap-

proximately one half of this subgroup initiated the use of these methods of weight control before treatment; the other half started them only after treatment had started. Four individuals (9%) were still using laxatives to control weight at follow-up. In contrast, 10 subjects (22%) were still vomiting at follow-up; 6 had used this method of weight control before treatment, but 4 had not begun to vomit until after treatment started. Three of the 4 who were using laxatives were also vomiting to control weight. The use of ipecac, diuretics, or appetite suppressants was rarely reported, as expected in a group of patients who primarily restrict intake.

A significant crossover to binge eating (bulimia) did occur over the course of treatment. Only 6 subjects (13%) had given a history of any binge eating before treatment began. Of those 6 subjects, three still reported binge eating at least once a week. However, almost half (22) of the total group had begun to binge eat after entering treatment; 10 of them still engaged in binge eating at least once a week. Of the 13 subjects who reported current binge eating, 8 (62%) were also vomiting at least once a week to control weight. In summary, dieting tended to normalize, with only a quarter of the group restricting their intake daily at follow-up. Likewise, compulsive exercising decreased by half. However, binge eating, vomiting, or both were dysfunctional eating behaviors that developed during recovery from restrictive anorexia nervosa in almost half of the subjects.

Education

Thirty-nine of the 41 individuals old enough to have graduated from high school had done so. One of the 2 high school dropouts planned to return to school. Of those 29 subjects old enough to have graduated from college, 20 (69%) had completed some post-high school education, 12 (41%) had completed college, and 6 (21%) had gone on to graduate school. Their fields of study included education, medicine, nursing, nutrition, and business. Despite the high level of education already attained, 44 (90%) of the 49 total subjects had plans to continue their education. In addition, 17 (71%) of 24 subjects enrolled in school also had part-time employment.

More than one third of subjects (17 of 49) reported having had problems in school as a result of their eating disorder. Problems included being preoccupied with their weight, having difficulty concentrating, and missing school because of hospitalization.

Employment

At follow-up, 39 subjects (80%) were employed at least part time. Seven of 10 unemployed subjects were full-time students. The remaining 3 individuals who were neither employed nor in school were all caring for their children at home. Among the 21 subjects who were not in school but who were employed outside of the home were 3 teachers, 2 nurses, 2 business managers, a nutritionist, and an investment broker. Overall, 5 subjects worked in food-related services full time.

In contrast to education, only 8 (16%) of 49 subjects reported having had difficulty finding or maintaining employment because of their anorexia nervosa. Five (62%) of these 8 also experienced problems with school. Overall, 4 subjects noted how their compulsivity and rigidity had diminished their efficiency and satisfaction at work. Two subjects felt limited by their diminished physical capacity; 1 subject who developed bulimia nervosa had difficulty because of binge eating at work as an ice cream vendor. Concerns about the types of jobs available to adolescents (mostly low-paying jobs related to food that present little challenge or potential for advancement) were expressed by 62% of those having trouble with work.

GAS Scores

The GAS outcome category could be determined for 48 subjects; the patient who died was included in the "poor" category. More than half (55%) of the subjects had an excellent outcome by GAS standards. Fourteen (31%) were in the "much improved" category, while 7 (14%) were in the "symptomatic" or "poor" group. The overall mean GAS score was 3.53 ± 3.3 . The average GAS score for those 16 subjects weighing less than 90% of their IBW was 6.00 ± 3.3 , significantly higher than the score of 1.96 ± 2.5 for the 25 normal-weight subjects ($t = 5.0$; $P < .01$).

In general, the six surviving patients rated as symptomatic or poor felt "trapped" by their illness and realized that weight loss could not solve their problems but could find no way to give up their eating disorder. Their dissatisfaction was not with feeling overweight, but with feeling powerless to control their weight. Four of the subjects in this group were vomiting daily at follow-up, and the individual who had committed suicide was driven to this act by her inability to stop vomiting. The remaining two subjects in the poor-outcome group were engaged in severe daily dietary restrictions.

Although only 21% of the total sample reported vomiting at follow-up, five (71%) of the group with a GAS score of 8 or higher reported vomiting. The mean GAS score of the vomiting group was three times that of the nonvomiting group (7.5 ± 2.7 vs 2.4 ± 2.6 ; $t = 5.5$; $P < .01$). The presence of binge eating at least once a week was only slightly less ominous and was generally associated with vomiting as well. The mean GAS score of the group that binged was 6.5 ± 3.3 , while those who did not binge averaged 2.1 ± 2.2 ($t = 5.0$; $P < .01$).

COMMENT

Anorexia nervosa traditionally has been considered a chronic condition with a variable, but generally poor, prognosis. A pediatric reference text recently summarized, "after 5 years, approximately one-third of the patients are symptom-free, one-third of the patients have symptoms but are functioning well, and one-third of the patients are still incapacitated."¹⁸ The data supporting this bleak outlook generally

come from reports of psychiatric-based treatment, in which consultation is often delayed by several years after the initiation of symptoms.¹²

Nussbaum and colleagues¹⁰ reported the first short-term outcome study of anorexia nervosa treated on a general adolescent medical service. Overall, 71% of the sample of 63 adolescents had a satisfactory outcome (GAS score, < 8), with a group mean GAS score of 5.8. That was significantly less than the 8.4 GAS score reported by Garfinkel and colleagues¹¹ in their psychiatric follow-up study. Notably, Garfinkel and associates' subjects were more severely ill than either those of Nussbaum et al or the present study group: 55% of subjects had had one or more previous admissions for the treatment of anorexia nervosa, more than 3 years had elapsed from symptom onset to consultation, and the mean body weight of the group on entry into care was only 64.9% of normal. In contrast, only 51% of Nussbaum and associates' subjects were hospitalized, and they averaged slightly more than 1 year from symptom onset to treatment. The present study group had been dieting, on average, only 1.6 ± 1.2 years before the first hospitalization.

Nonetheless, the mean GAS score of 3.5 ± 3.3 in our sample was significantly lower than those in both of these reports ($P < .01$), with a satisfactory outcome in 86% of our subjects. Although all of our subjects were hospitalized, at follow-up only 29% were binge eating and 27% were restricting food intake daily. These apparently better results may be due to different sample characteristics, different treatment methods, or a longer follow-up interval. We found, as have others, that vomiting (reported by 21%) and, to a lesser extent, binge eating (reported by 29%) were associated with an unsatisfactory outcome.

The mortality of less than 4% is similar to that in other reports in the literature.⁸ Close medical surveillance should eliminate death due to malnutrition. Death by suicide, on the other hand, is more difficult to control and has become the most common cause of death among persons with eating disorders. The only known death in our sample was due to suicide.

Our treatment emphasizes develop-

mentally oriented, multidisciplinary care based in pediatrics. After discharge from the hospital, subjects were followed up as outpatients for varying lengths of time, receiving various types of medical, psychological, and pharmacologic treatment as dictated by their specific needs and course of illness. Almost all subjects received individual psychotherapy, and almost half participated in family therapy. Treatment was provided by a variety of professionals, including psychiatrists, psychologists, and, social workers, for varying lengths of time. Because of the number of different forms of treatment and the small sample size, it is impossible to determine outcome in relation to treatment modality or duration. Although treatment does tend to be prolonged, it does not continue indefinitely. It is encouraging to find that the most commonly used prescription medicine by our patients with anorexia nervosa was oral contraceptives, one of the most commonly prescribed medications for all women in this age group. The general lack of medications and of symptoms speaks to the overall well-being of the group at follow-up. Almost three fifths of the sample reported no significant health problems after discharge from the hospital. When symptoms or morbidity did occur after hospitalization, they were most commonly referable to the gastrointestinal tract. Chronic constipation, irritable bowel syndrome, or peptic ulcer disease was reported by a quarter of the subjects. In both subjects with peptic ulcer disease, the duodenal lesion was diagnosed when the ulcer perforated, requiring emergency surgery. There were no recognized factors predisposing to perforation in either of these subjects. Involuntary esophageal reflux and dental enamel erosion occurred in subjects with chronic vomiting, as expected.¹⁴

The primary physiologic dysfunction related to anorexia nervosa that concerns most parents and many patients is amenorrhea and the possibility of infertility. Our data are encouraging in both respects. Of the subjects who developed anorexia nervosa before menarche, 73% eventually began to menstruate. More than 81% of those with secondary amenorrhea resumed menstruating.

The common factor for initiation or

resumption of menstruation appeared to be attaining a weight that was approximately 90% of IBW for height. The average weight in the amenorrheic group was significantly less than that in the menstruating group. Gaining weight appears to be a necessary, but not always sufficient, factor in resuming menstrual periods, however. One subject was amenorrheic for more than 6 years. During the last 2 years of that interval her weight did not change appreciably, but she was enrolled in medical school and under a great deal of stress. She attributed the eventual return of her periods to being more relaxed and having stable interpersonal relationships.

This study cannot fully address the issue of infertility in anorexia nervosa, since not all of the subjects were sexually active or desiring to become pregnant. Of the 15 known pregnancies in nine subjects, 2 ended in elective abortion, 3 were ongoing at the time of follow-up, and 10 went to term delivery. The seven subjects who carried their 10 pregnancies to term all had newborns with no perinatal or neonatal complications. Both of the complicated pregnancies occurred in the same subject, with no other subject reporting difficulty with pregnancy or delivery.

No subject who desired to become pregnant had been unable to do so. One nulliparous subject who wanted to have a child was not considered infertile at the time of data collection since she had stopped taking birth control pills only 8 months previously; she became pregnant 4 months later.

Just as menstruation tended to normalize, so did eating habits. At follow-up only a quarter of the sample practiced daily dietary restriction. This probably reflects the dieting habits of older adolescent and young adult women in the general population. Interestingly, only one of the six overweight individuals was dieting at follow-up. Many of the subjects reported still being concerned about their weight, even though this issue did not control their lives as it had when the eating disorder was active. Again, this may reflect a cultural bias toward thinness experienced by many girls. Several individuals remarked that they did not believe that it was possible to be "cured" of their

eating disorder, likening it to alcoholism. They continued to harbor negative thoughts about weight and used weight loss to cope with stress, even though there was no evidence of active disease. The majority did believe, however, that they had or could overcome their disorder and lead normal lives. A small number of subjects continued to have serious problems with eating and weight control. Two subjects were on severely restrictive diets. The other surviving four subjects in the "poor" outcome category all had pernicious bingeing and vomiting. All of the subjects with poor outcome appeared to have entered a "chronic" phase of their eating disorder, with little perceived hope of recovery.

A bothersome finding was the high rate of crossover to binge eating, vomiting, or both (generally not seen in restrictive anorexia nervosa) after treatment began. Binge eating was initiated in approximately one half, and vomiting in one quarter, of the subjects. Although the majority had since stopped, there were still 10 subjects binge eating and 4 vomiting to control their weight. Of the 6 subjects who weighed more than 110% of their IBW, 5 developed binge eating after hospitalization, and 3 continued with it.

What makes these practices especially vexing is the implication by some patients that their habits developed as a complication of treatment. They perceived that they were expected to "eat their way out of the hospital" and would sometimes gorge themselves to "make weight." Of course, binge eating and vomiting may be a part of the natural course of anorexia nervosa for some patients. The literature suggests that 20% to 50% of subjects diagnosed as having anorexia nervosa eventually develop bulimic symptoms.^{15,16} The clear message for clinicians, however, is that gaining weight should not be the sole focus of treatment and that unhealthy eating patterns (whether eating too little or eating too much) should be avoided, if possible.

The eating disorder did not appear to have a significant impact on ultimate educational or employment goals. The high level of education either attained or planned is in concert with the striving for achievement that is so characteristic of persons who develop anorexia ner-

vosa. In many cases their perfectionism prevents them from being able to live up to their expectations, however. A theme expressed by more than one third of the group was difficulty concentrating or paying attention in school, attributed either to low weight or preoccupation with weight. Few subjects had any difficulty finding or maintaining a job. Concern was expressed about the types of jobs available to young people with few work-related skills, with a perception that most jobs were in food-related services.

There are limitations to this present study. The data are primarily retrospective self-reported variables, with the obvious potential for overreporting or underreporting. In several cases, parents were also interviewed. We found no evidence of discrepancies between parental and patient reports. Historical data that could be corroborated in the chart were also reported accurately. Although weights were not actually measured, there was no evidence of systematic bias in the reporting of this value. Eleven patients had recent weights recorded in their medical record, with excellent agreement with

their self-report.

Several positive features of the study subjects should be emphasized. First, they constitute a homogeneous sample of adolescents with anorexia nervosa. Those who met criteria for bulimia nervosa only (who might have been included in outcome studies of anorexia nervosa before 1987) were excluded. Second, their interviews were conducted by a medical student who did not participate in the care of the patients. This lessens, but does not eliminate, potential reporting bias. Third, the sample included all patients with anorexia nervosa admitted to our pediatric service during a 6-year period. These patients were generally admitted because of extremely low weight or because of failure of outpatient treatment. Thus, our encouraging results may represent a conservative estimate of outcome. Fourth, all but eight of the patients were cared for primarily by one pediatrician; although this may limit data generalizability, it does ensure relative consistency in the treatment approach that patients received.

Our data suggest that adolescents with anorexia nervosa can be treated

successfully with a developmentally oriented, multidisciplinary approach that includes inpatient and outpatient management based in pediatrics. The overwhelming majority of patients can expect to return to normal weight and menstrual functioning, with no evidence of infertility in those whose menstrual periods return. In general, long-term achievement in education and employment do not appear to be adversely affected. Fewer than 15% of patients had severe, ongoing problems with their eating disorder. Health care providers caring for adolescents with anorexia nervosa need to be aware of the tendency to cross over to binge eating, vomiting, or both, with a negative effect on outcome. Further studies regarding the long-term efficacy of various treatment modalities and the long-term implications of various behavior patterns are required.

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In Other AMA Journals

JAMA

Are Clinical Trials a Cost-effective Investment?

A. S. Detsky (JAMA. 1989;262:1795)

Aminoglycoside Ototoxicity in Cystic Fibrosis

Evaluation by High-Frequency Audiometry

Teresa I. McRorie, PharmD; John Bosso, PharmD; Loren Randolph, MS

• In this study, we sought to determine the clinical usefulness of high-frequency audiometry (8000 to 20 000 Hz) in detecting aminoglycoside-induced increases in pure-tone hearing thresholds before they are noticed in conventionally tested frequencies. We measured hearing thresholds from 250 to 20 000 Hz in 22 patients with cystic fibrosis who were treated with aminoglycosides. The audiograms were age-matched and were compared with those from 13 patients with cystic fibrosis and 38 subjects without cystic fibrosis, all of whom had never received aminoglycoside therapy. In patients with cystic fibrosis who were treated with aminoglycosides (younger than 20 years), there were statistically significant elevations only in frequencies higher than 16 000 Hz. Patients with cystic fibrosis who were treated with aminoglycosides who were 20 years and older had elevated thresholds in all frequencies tested. Patients with cystic fibrosis who were not treated with aminoglycosides did not differ statistically from controls. High-frequency audiometry may serve as a useful measure of elevation in pure-tone hearing thresholds that precede noticeable loss of auditory acuity in patients with cystic fibrosis who are receiving long-term aminoglycoside therapy.

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The ototoxic and nephrotoxic potential of aminoglycoside antibiotics was revealed in the first case reports of aminoglycoside efficacy.¹ With time,

vestibular and auditory toxicity became widely known potential side effects associated with administration of compounds in this class. Using only conventional audiometry (frequency ranges, 250 to 8000 Hz), Moore et al² reported a 22.3% incidence of ototoxicity in a study of 135 patients receiving aminoglycoside therapy. Unfortunately, by the time conventional audiometry detects hearing loss, the damage is often clinically significant. Unlike aminoglycoside-induced nephrotoxicity, there is no routine indicator of subclinical ototoxic damage.

Cochlear damage caused by aminoglycosides begins at the base of the cochlea and continues toward the apex with continued exposure.³ High-frequency hearing loss is the initial manifestation of this insult, with subsequent loss in the lower frequencies. Hearing loss, as detected by pure-tone audiometry, is traditionally defined as an elevation of hearing thresholds in the conventional frequency ranges (250 to 8000 Hz) of 15 dB or more in at least two frequencies tested. This definition and the clinical significance of such loss is less clear in the frequencies above 8000 Hz.⁴ However, the knowledge that threshold elevations in the high frequencies precede conventional-frequency hearing loss with aminoglycoside exposure make it desirable to evaluate the clinical utility of high-frequency audiometry.

New calibration and instrumentation techniques have aided in the development of high-frequency audiometers with which reproducible hearing thresholds can be obtained in the clinical setting.⁴ Dreschler et al,⁵ using the calibration technique developed by Fausti et al,⁴ tested 100 ears of patients before and after the patients received a platinum derivative known to produce high-

frequency hearing deficits.⁶ A 58% incidence of hearing loss in the frequency range above 8000 Hz was demonstrated, compared with a 44% incidence if only those frequencies at 8000 Hz or lower had been assessed. These observations support the use of high-frequency audiometry in the early detection of hearing loss from ototoxic agents that initially insult the basal portion of the cochlea. It would be desirable to detect the damage when it is only in the high frequencies before the damage extends into the conventional ranges where the perception of speech is affected.

In previously published studies,^{6,7} hearing loss secondary to ototoxic stimuli was assessed by comparing one-time patient audiograms with those of individuals not exposed to ototoxic stimuli. Our study utilized an analogous study design to evaluate the effects of aminoglycosides in patients with cystic fibrosis on hearing thresholds in both conventionally tested and high-frequency ranges.

PATIENTS AND METHODS

Patients older than 6 years seen at the cystic fibrosis clinic at the University of Utah Medical Center, Salt Lake City, from August 1986 through March 1987 were considered for participation in the study. Responses in children younger than 6 years were considered unreliable due to potential inability to cooperate with testing procedures. In previous studies, it has been found that age but not sex is associated with differences in hearing in young adults.^{8,9} Therefore, healthy, age-matched volunteers were used as controls. Two controls per patient were used to increase the statistical power of the analysis of the differences between the two groups. The majority of the control subjects worked at the hospital or were children of employees and were not considered experienced listeners. Subjects signed a consent form that along with our protocol was approved by the local institutional review board. All subjects

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were interviewed by the audiologist administering the test for factors known to contribute to hearing loss. These exclusion criteria included history of head trauma, severe noise exposure, ear surgery, chronic ear infections, meningitis, premature birth, hyperbilirubinemia, or family history of hearing loss. Patients and controls whose medical histories were unknown or in question were also excluded from the investigation. A period of at least 2 weeks between the last course of aminoglycoside therapy and the audiometric examination was required to reduce the detection of a temporary threshold shift.¹⁰

Thirty-eight patients with cystic fibrosis were evaluated audiometrically. Three patients were excluded after evaluation. One was excluded due to known concurrent severe noise exposure, one due to asymmetric loss in high frequencies in the left ear from unknown causes, and one due to persistently abnormal tympanometry readings after tympanic perforation. Twenty-two patients had received aminoglycosides. All of these had received at least one course of tobramycin sulfate therapy. The other aminoglycosides received were amikacin sulfate, netilmicin sulfate, and gentamicin sulfate. Thirty-eight control subjects were studied. The patients and controls were divided into six groups for analysis of the effects of a positive history of aminoglycoside exposure on hearing threshold. Patients with cystic fibrosis were divided into four groups based on the presence or absence of aminoglycoside exposure and an age of 20 years or younger. The choice of division of ages was based on the Osterhammel and Osterhammel⁹ study on age and sex variations in high-frequency hearing. The control subjects were divided into two groups based on age. The mean age, number of patients, and number of subjects per group are presented in Table 1. It should be noted that there were only three subjects in the cystic fibrosis group that had not received aminoglycosides and were older than 20 years.

The test site was the University of Utah Otolaryngology Clinic, Salt Lake City, using the IAC model 403 sound-treated booth. Ambient noise levels were measured with a model 800B sound-level meter (Larsen-Davis, Provo, Utah) and were well within the levels specified by the American National Standards Institute SC.1-1977 standards.¹¹ These standards are not applicable to frequencies higher than 8000 Hz, but there was no measurable ambient noise in the frequencies above 8000 Hz. The test equipment included a model 702 impedance bridge (Amplaid, AND-OR Distributors, Golden, Colo), a model 1704 clinical audiometer (Grason-Stadler, AND-OR Distributors), and a model 20-K high-frequency audiometer (Demlar, Chapel Hill, NC). The Grason-Stadler audi-

	No. of Ears	Mean Patient Age, y
Patients aged 6-19 y		
Patients with cystic fibrosis		
Treated with aminoglycosides	24	13
Not treated with aminoglycosides	20	10
Controls	36	11
Patients ≥20 y		
Patients with cystic fibrosis		
Treated with aminoglycosides	20	25
Not treated with aminoglycosides	6	25
Controls	40	25

	No. of Patients With Cystic Fibrosis by Age (No. of Ears)				No. of Controls by Age (No. of Ears)	
	6-19 y (24)	6-19 y (20)	≥20 y (20)	≥20 y (6)	6-19 y (36)	≥20 y (40)
Hearing threshold level, Hz						
4000	2.9 (5.9)	3.5 (6.5)	19.7 (28.1)	14.2 (9.7)	4.4 (5.6)	3.5 (8.2)
6000	9.0 (8.7)	6.8 (9.6)	28.0 (29.1)	25.8 (15.3)	8.5 (5.8)	8.9 (9.2)
8000	10.6 (8.2)	8.5 (9.1)	27.0 (30.3)	11.7 (13.1)	9.0 (8.9)	5.8 (8.9)
Sound pressure level, Hz						
16000	54.7 (20.6)	48.3 (15.6)	82.4 (17.8)	77.3 (20.0)	50.0 (21.0)	60.5 (21.0)
17000	67.8 (16.6)	55.5 (15.3)	90.2 (13.0)	86.2 (16.8)	57.5 (20.7)	73.1 (19.0)
18000	80.0 (15.9)	68.0 (17.0)	95.6 (6.0)	94.3 (7.2)	69.6 (21.7)	85.5 (15.2)
19000	89.8 (14.2)	76.6 (17.3)	98.1 (2.8)	99.0 (0.0)	80.7 (19.2)	92.3 (11.0)
20000	94.3 (10.6)	82.0 (16.9)	98.0 (2.9)	99.0 (0.0)	85.8 (15.1)	95.1 (4.9)

*Values are given as mean (SD).

ometer was equipped with TDH-39 earphones in MX-41/AR cushions and was calibrated to American National Standards Institute S.3-1969 standards.¹² The Demlar audiometer was equipped with model HV/1A earphones (Koss). The calibration of these earphones ensured that the output at each frequency, in terms of decibel sound pressure level, was the same as dial value. Frequency was measured and found to be within 3% of dial value. All calibration was accomplished using the Larsen-Davis model 800 sound level meter and associated 1.27-cm microphone and the coupler described by Fausti et al.⁴ Calibration was checked approximately every 2 months throughout the course of this study to ensure accuracy of the stimuli.

To avoid any contamination of the data from an underlying outer- or middle-ear dysfunction, an otoscopic examination was performed followed by tympanometry and acoustic reflex testing. Patients with abnormal tympanograms or absent acoustic reflexes were rescheduled for testing at a later date. Pure-tone air-conduction thresholds were determined in both ears at 250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz with the Grason-Stadler audiometer. These were measured using hearing threshold level units and converted to sound pressure level

units for use in the graphic comparison of high and conventional frequencies. Thresholds at frequencies of 8000 to 20 000 Hz were determined at 1000-Hz intervals using the Demlar audiometer. All thresholds were obtained using the procedure recommended by Carhart and Jerger.¹³ Each subject was given conventional audiometric instructions, and all audiometric testing was done by one of two professional audiologists holding the Certificate of Clinical Competence from the American Speech-Language-Hearing Association.

Descriptive statistics were used to represent the data. Additionally, paired *t* tests were performed to evaluate any difference between the left and right ears, to allow the data from both ears to be combined if there was no difference noted. A 99% level of confidence was used. Tests of significance were performed for each frequency where the number of subjects in each group was greater than 10. Because normal distribution cannot be assumed with a small number of subjects, the nonparametric Mann-Whitney *U* Test was used with a 95% level of confidence. Subjects whose hearing threshold exceeded the maximum output tested at any frequency were assigned a value of 99 dB for that frequency. For each frequency, the number of ears assigned this value was recorded.

A comparison of the differences between groups was performed with one-tailed Mann-Whitney *U* Tests. To preclude the possibility of detecting a difference between groups at any frequency as a chance result of performing multiple tests, the number of frequencies at which a comparison was made was limited. Subject groups were compared at 4000, 6000, and 8000 Hz measured with the Grason-Stadler audiometer. For those frequencies measured with the Demlar high-frequency audiometer, groups were compared at 16 000, 17 000, 18 000, 19 000, and 20 000 Hz.

RESULTS

Student's paired two-tailed *t* test was performed using trimmed means to detect any difference between the left and right ear. A difference was noted at the 13 000-Hz frequency in the control group ($P = .01$). Because no other differences were noted, the data are represented with results from both ears combined. The mean hearing thresholds and SDs for each frequency are presented in Table 2. These data are graphically displayed in Fig 1.

Patients Aged 6 to 9 Years

There were no statistically significant differences ($P \geq .15$) noted between patients with cystic fibrosis who had not received drug therapy ($n = 15$) and the normal subjects ($n = 18$). The data from these two groups were thus combined and compared with those from 12 patients who had received aminoglycosides. Differences between the two groups were noted at the four highest frequencies with $P \leq .009$ at frequencies of 17 000 to 19 000 Hz and $P = .00005$ at 20 000 Hz.

Patients Aged 20 Years and Older

There was an insufficient number of patients in the cystic fibrosis group who had never received aminoglycoside therapy to perform inferential statistical analysis with this group separately ($n = 3$). Therefore, in the older group, only control subjects ($n = 20$) were compared with patients with cystic fibrosis who had received aminoglycoside therapy ($n = 10$) to detect any statistically significant elevation in hearing thresholds. Differences between the two groups were noted at all frequencies tested. The level of significance was less than .001 for all of the frequencies in the con-

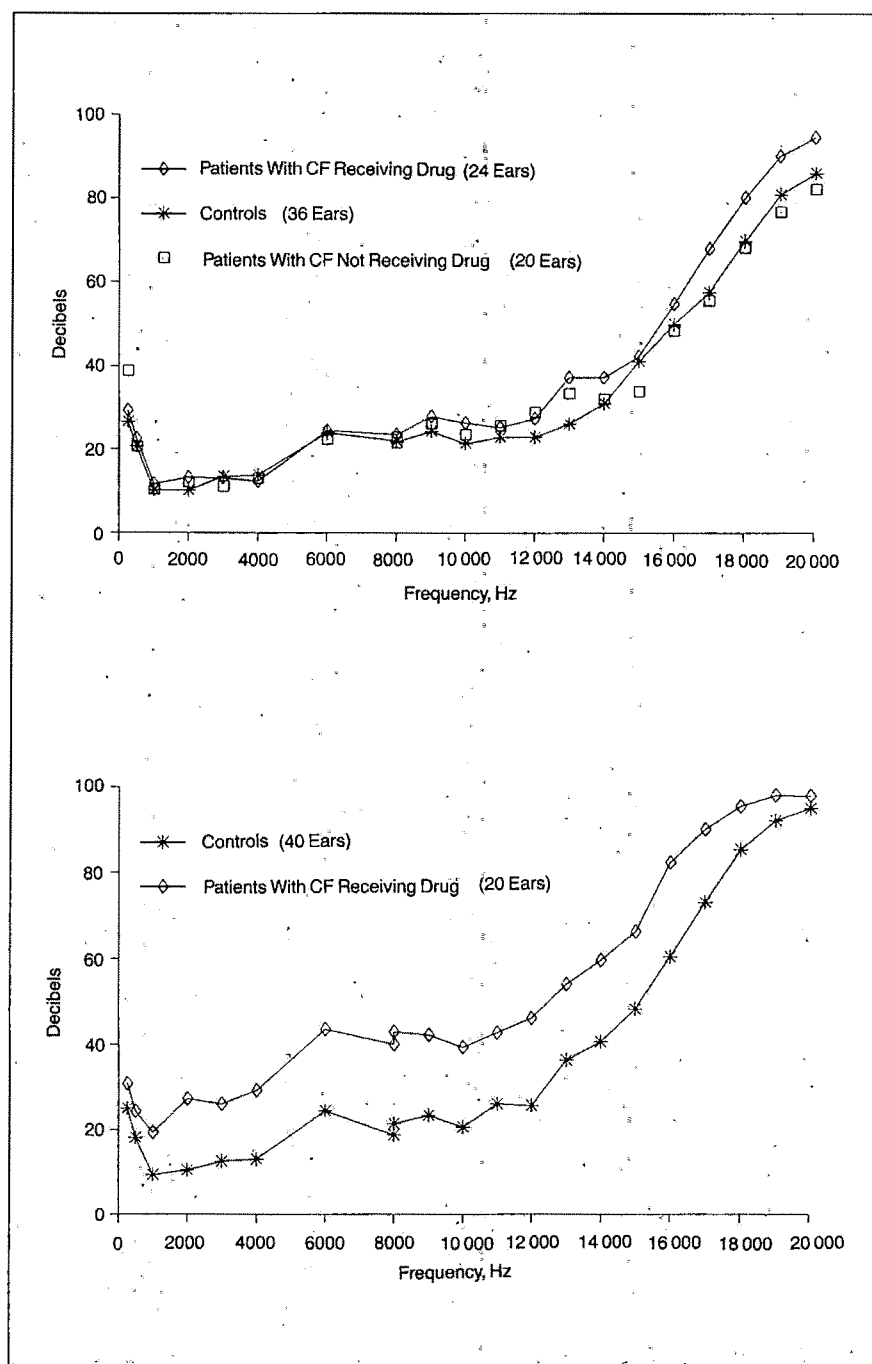


Fig 1:—Mean hearing thresholds measured at 250 to 8000 Hz with a Grason-Stadler audiometer and 8000 to 20 000 Hz with a Demlar audiometer. Conventional hearing threshold levels were converted to sound pressure level for ease of comparison. CF indicates cystic fibrosis. Top, Patients aged 6 to 9 years. Bottom, Patients aged 20 years and older.

ventional ranges and at 16 000 Hz and 17 000 Hz. The differences at frequencies of 18 000 Hz through 20 000 Hz reached significance at .005.

In Fig 2, the number of patients in both age groups who did not hear at the maximal output of the audiometer at the

individual frequencies is displayed. The number of patients who did not hear at a given frequency was greater in the groups that had received aminoglycoside therapy than in those who had not. This was true for all frequencies except 19 000 and 20 000 Hz in the older age

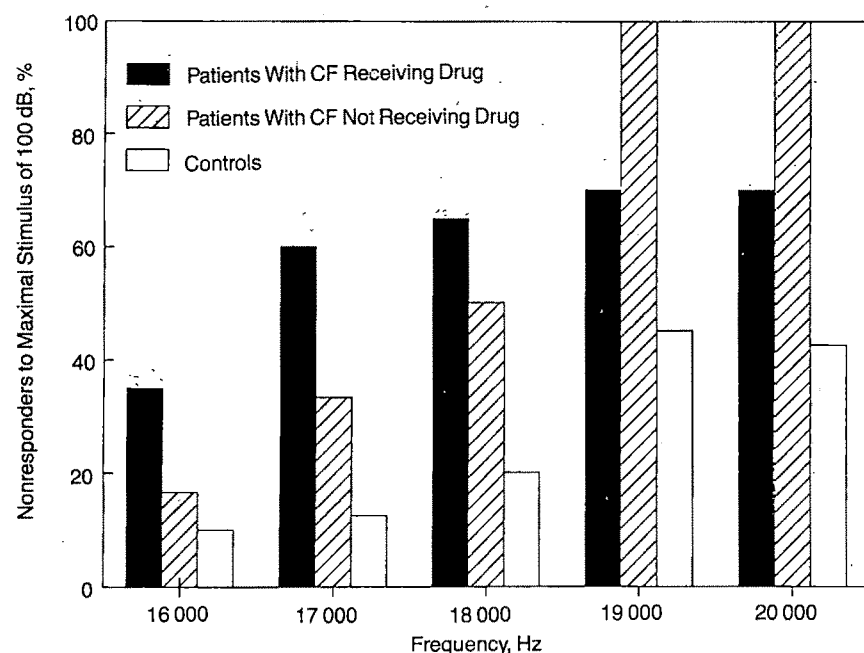
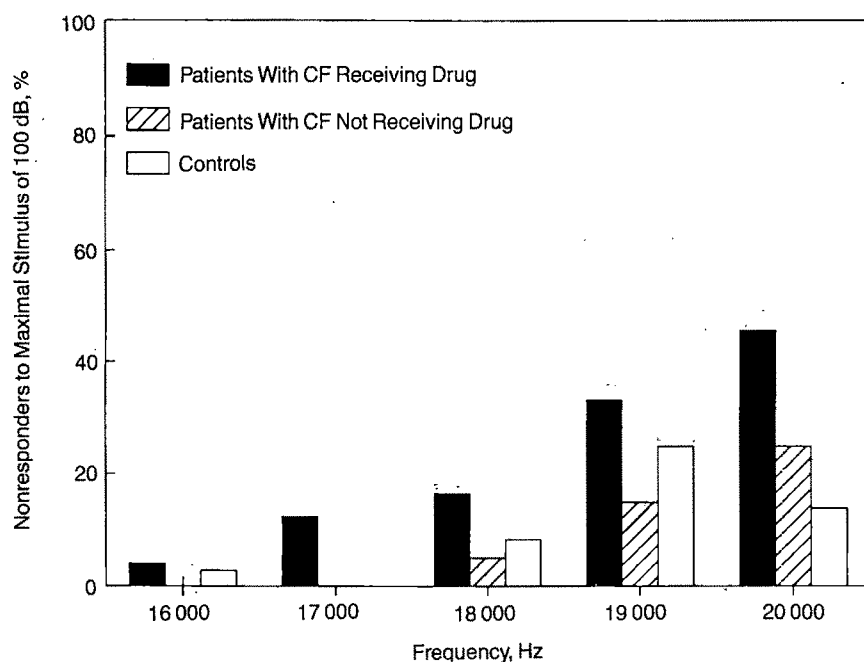


Fig 2.—Graphs representing the percentage of patients who did not respond to maximal stimulus of 100 dB. CF indicates cystic fibrosis. Top, Patients aged 6 to 19 years. Bottom, Patients aged 20 years and older.

group. Two patients in the older age group who had received aminoglycoside therapy had hearing deficits that extended into the frequencies below

15 000 Hz. The patients had received prolonged single courses of tobramycin therapy extending 4 months in one patient and at least 9 months in the other.

COMMENT

We found that those patients with cystic fibrosis aged 10 through 19 years who had received aminoglycoside therapy had statistically significant elevations of mean hearing thresholds in the frequencies from 16 000 Hz through 20 000 Hz when compared with controls. There were no differences in the mean hearing thresholds between the control groups and patients with cystic fibrosis who had not received aminoglycoside treatment. For those patients with cystic fibrosis older than 20 years, higher mean hearing thresholds for all frequencies tested were noted when compared with control subjects.

There are limited data for normal hearing thresholds in the frequencies above 8000 Hz. Studies establishing normal values have been performed, but a firm definition of normal hearing has not yet been determined.^{8,9,14,15} This is partly due to varying methods and instrumentation and is also largely due to the small number of ears tested to date.¹⁶ A criterion for defining high-frequency hearing loss secondary to ototoxicity is still debated due to a lack of normative data. Our data confirm values previously obtained in healthy volunteers and contributes to the normative database. In 1979, Osterhammel and Osterhammel,⁹ using a different method of determining high-frequency thresholds that incorporated a quasi-freefield technique in a soundproof booth, tested the hearing of 286 control subjects, 67 between the ages of 10 and 19 years, and 44 between the ages of 20 and 29 years. Mean high-frequency thresholds for their 10- to 19-year-old age group were in agreement with the findings in the control groups of our study. The SDs ranged from 6.6 to 19.5 dB, compared with our range of 5.9 to 21.7 dB. It should be noted that the small SDs may be an erroneous finding in the highest frequencies because a large percentage of patients did not hear at the maximal output. The means and SDs for the older age group are also consistent with the present findings, with SDs ranging from 6.8 to 16.4 dB compared with 4.9 to 21.1 dB in the present study.

Pedersen et al¹⁶ used the data from the Osterhammel and Osterhammel⁹ study to compare the long-term effects

of aminoglycosides in patients with cystic fibrosis. Forty-six patients with cystic fibrosis who had received aminoglycoside therapy were evaluated audiometrically using the same technique used by the Osterhammels in their normative study. Their criterion for determining hearing loss with one audiometric examination was not defined and it was not indicated if they used statistical methods to compare the two groups. They found that two patients had hearing loss that was attributed to tobramycin therapy. These two patients were the only patients found to have total hearing loss at some frequencies, which is markedly different from findings of our study. It is possible that this discrepancy is due to the use of a lower maximal output (decibels) in our study. More likely explanations of the differences in the findings may lie in the

potential differences in the type of overall administration of aminoglycosides to patients with cystic fibrosis in Denmark¹⁶ compared with our program.

We cannot conclude from our data that the elevations in hearing thresholds observed can be entirely attributed to aminoglycoside exposure. We did, however, control for variables that are also associated with ototoxicity. Additionally, our findings are consistent with the trends observed with the use of aminoglycosides in this population. The younger patients had, on average, received fewer aminoglycosides than the older subjects and, therefore, could be expected to have smaller hearing threshold elevations than the older patients. To accurately identify the extent to which aminoglycosides damage hearing over time, an analysis of the total amount of each of the individual amino-

glycosides received along with the time course the drug was delivered is required.

It is important to note that elevation of pure-tone hearing thresholds alone does not define hearing loss.¹⁷ However, it is known that this is the first clinically detectable sign that precedes hearing loss.¹⁰ Because of this, the differences noted in the younger age group at the highest frequencies are particularly important. High-frequency audiometry should therefore be evaluated to assess whether cessation or alteration of aminoglycoside use in patients with threshold elevations at frequencies above 8 000 Hz will prevent hearing loss in the conventional frequencies.

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In Other AMA Journals

ARCHIVES OF DERMATOLOGY

Chancroid: A Newly Important Sexually Transmitted Disease

Allan R. Ronald, MD, Francis Plummer, MD (*Arch Dermatol.* 1989;125:1413-1414)

Nodular Fasciitis on the Palm of a Child

Conrad Brimhall, MD; Annette D. Segura, MD; M. Kathleen McTigue, MD; Nancy B. Esterly, MD (*Arch Dermatol.* 1989;125:1441)

Educational Interventions



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Purpose.—This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.

Editorial Comment.—*You probably have a very efficient method for scheduling your patients. This has not been so easy in training program ambulatory clinics, due to variable resident levels and experience levels. The solution—computerize the system. This article shows that it can be done.*—H.D.A.

Computerized Patient Scheduling in Outpatient Residency Practices

Thomas G. Quattlebaum, MD

• A computerized appointment system is described that accommodates the special needs unique to residency training programs. Appointments are scheduled automatically according to the type of problem with which the patient presents to the office as well as the differing time requirements of faculty physicians and residents at various levels of training. The system provides for the easy and flexible scheduling of residents and the automation of appointment reminders.
(AJDC. 1989;143:1333-1336)

Patient appointments are an important part of the outpatient practice of medicine and provide benefits for both patient and physician. An effective scheduling system should allow the provision of care in the most efficient fashion for both medical staff and patients. It is widely recognized that prolonged waiting is a major cause of patient dis-

satisfaction. An ideal appointment system should keep waiting to a minimum while still providing the most efficient use of office staff and space and maximizing the number of patients that can be seen in a time period.

Several major methods are used for scheduling patients.¹⁻⁶ With the block scheduling technique, all patients are appointed for the same time. For example, all morning patients may be asked to come at 8 AM and all afternoon patients at 12:45 PM. Many traditional hospital outpatient clinics have employed this system. Although it can provide a continuous flow of patients for the medical staff, block scheduling leads to very long waiting periods for many patients.

A modified block schedule breaks a session into smaller blocks. For example, one group of patients may be scheduled at 8 AM, with other groups to arrive at hourly intervals throughout the day. Wave scheduling is a variation of the modified block system in which patients are appointed in several "waves" of more than one patient throughout an hour, usually with time at the end of

each hour for the physician to complete the care of patients appointed for that hour. Both of these methods can reduce the prolonged waiting of a block schedule, but each involves a built-in waiting time at the beginning of the hour or wave. In addition, neither method considers the time requirements of a particular patient or physician.

Individualized appointment systems give a different appointment time to each patient. Structuring the schedule so that the length of an appointment reflects a patient's presenting problem has been shown to reduce waiting times and increase patient satisfaction.^{2,6}

Outpatient scheduling in a residency program presents unique problems that are not present in a practicing physician's office. Now that many residency programs have reorganized their traditional outpatient clinics into continuity-based programs, these practices often have faculty physicians as well as interns, residents, and physician extenders seeing patients in the same outpatient location at the same time. Thus, physicians of widely varying skills are

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usually practicing simultaneously in the residency program's outpatient service. The length of time allocated for patient visits ideally should reflect not only the types of problems with which the patient presents to the office but also the skills and proficiency of the physician seeing the patient. For example, an inexperienced intern often needs to discuss a relatively simple follow-up visit with an attending physician. He may require considerably more time to complete that visit than a senior resident seeing a far more complex patient with multiple medical problems.

The variable time that residents spend in the outpatient practice from month to month causes another practical difficulty in designing a patient scheduling system. For example, a resident may be in the practice only 1 half day each week while doing an intensive care rotation but 3 or more half days during the following month.

A patient scheduling system for a residency program should consider the varying needs of both patients and physicians while maintaining the timely flow of patients in the practice. It should also allow quick and flexible scheduling of residents. An ideal system would also provide for the automated printing of appointment reminders. Herein, a computerized scheduling system for microcomputers is discussed that meets these special requirements.

BACKGROUND

The pediatric residency program at the Medical University of South Carolina, Charleston, provides general pediatric training with an emphasis on primary care and continuity of care as well as traditional inpatient and intensive care experiences. A primary care practice provides the majority of the residents' experience in outpatient continuity of care. The practice consists of 3 full-time faculty attending physicians, 2 behavioral science faculty, a nurse practitioner, and 24 residents, as well as nursing and business office staff. Each resident spends part of every week in the practice seeing his or her own panel of patients. Residents spend from 1 to 4 half days each week in the practice, depending on their rotation for that month. An average of 25% of each house officer's time over 3 years is scheduled

in the practice. One or 2 attending physicians, the nurse practitioner, and 4 or 5 residents see patients during each half-day session. Behavioral science faculty see patients 5 half days during the week. Thus, a total of 8 or 9 health care providers are scheduled for each morning or afternoon session during the week.

From 1982 to 1985 a set of computer programs were developed that provided the foundation for the scheduling system. The initial programs were designed to allow the assessment and management of outpatient experiences in residency training.⁷ Billing programs were later integrated with the original programs. In 1984 and 1985 the computer system was enlarged and transferred from a mainframe computer to a microcomputer located in the practice.^{8,9}

SCHEDULING SYSTEM REQUIREMENTS

In 1986 a computerized scheduling system was developed to replace the previously used manual appointment book. A technical discussion of the design of the computer programs and the algorithms involved is beyond the scope of this article and is presented elsewhere.¹⁰ However, a general overview of the needs that determined the scheduling system's formulation is helpful in understanding the system's usefulness in a residency program.

A number of considerations led to the current system design. The simultaneous display of all physicians and their appointed patients was essential to allow a scheduling clerk to see at a glance where patients could be appointed. The system also needed to display comments for each physician and for each appointment.

A technique was needed to designate time slots that were allocated to a previous patient. For example, if a young infant were scheduled for a health maintenance visit with a first-year resident at 9:15 AM, some method was needed to show on the computer screen that the resident's time slots until 10:15 AM were assigned to that infant's well check and were thus not available for another patient appointment. Automatic computation of the differing periods needed for the various physician levels and patient types was vital for the proper functioning of the system.

A method was desired that would allow appointment reminders to be mailed selectively to patients who have an increased likelihood of missing their appointments.

Finally, easy scheduling of physicians was important. For instance, if a resident were assigned to the practice every Monday morning for a month, the system should be able to schedule all of these mornings with a single entry, rather than requiring a separate entry for each Monday. A similar ability was required for the removal of physicians from the schedule during their vacations.

TECHNIQUES USED

As shown in the Figure, the appointment entry screen used by the system displays the appointments for up to 12 physicians during a 1-hour block of time on a particular day. If more than 12 are scheduled, multiple screen displays are used to present the physicians in groups of 12 per display. Comments are displayed for each physician and are used to inform clinic personnel of each resident's current hospital or clinic rotation. This information is useful in appointing patients who make "call-in" sick visits when their assigned physician is not scheduled to be in the practice that day. These patients are usually appointed to residents on an outpatient clinic rotation.

Each July when new house officers join the residency program, their names are entered into the computer system with the date they joined the program and their residency level at that time. This information remains on file and is used by the computer to determine what a resident's level will be at the time of a future appointment. This level is used to determine the additional time needed for the type of appointment being scheduled. As seen in the Figure, the phrase "... same ..." is used on the screen to mark time slots that are committed to an earlier appointment.

APPOINTMENT ENTRY

When clerical staff wish to give an appointment to a patient, that patient's name or number is entered at the terminal keyboard. This information is checked for a match among patients defined to the system. If an exact match is

not found for alphabetical entries, a listing of patients with similar last names is displayed.

Comments are entered for each patient appointment and are used to designate for what type of visit the patient is scheduled. After the patient's name or number is accepted by the computer, the resident's level is computed. The comment for that appointment is then searched for key letters or phrases to determine the length of time required for that physician dealing with that problem. The time allocated for the various physician levels is summarized in the Table. The abbreviation WC is used to signal that the patient will be seen for a "well check" and should be given 60 minutes if the physician is a first-year

resident, 45 minutes for a second-year resident, and 30 minutes if the physician is a senior resident or an attending physician. "Brief visits" are allocated only one 15-minute time slot, regardless of the physician's level. The abbreviation WCF is used to designate the first of several well check appointments for a family. No additional time is given for these appointments beyond that allocated to subsequent family members. This technique allocates a first-year resident, for example, 1 hour for a well check if only one family member is seen and an additional 15 minutes if a second person is seen from the same family. Medical conferences are allocated 60 minutes for all physician levels. All residents are given a total of 80 minutes for

"return visits" and "sick visits," but faculty physicians are scheduled for 15 minutes for these appointments.

If the computer finds a conflict between the time required and previous or subsequent appointments, it does not allow the appointment to be entered. In addition, because several terminals can be used for data entry simultaneously, the system does not allow an appointment to be entered if it conflicts with one being entered at another terminal. Patients who need to be scheduled for immunizations, laboratory studies, etc, but who do not need to be seen by a physician are scheduled for the nursing staff. The comments for these appointments are helpful in alerting the nurses as to what studies or procedures are needed.

Function keys on the terminal keyboard allow appointment personnel to perform special tasks quickly. For example, if a patient requests an appointment with Dr X, one key is used to jump to the next session that Dr X is scheduled to be in the clinic. Another key is used to search the appointments on file to find when a patient has an appointment. This capability is useful when a patient calls to change an appointment but cannot remember the date. Another function key displays a month's calendar with the resident's sessions highlighted and notes the number of patients already appointed for each session. An additional key lists the information on file about a patient, including the assigned resident's name as well as the parent's name, address, and telephone number.

DOCTORS SCHEDULED ON MORNING WEDNESDAY 05 APR 89					
9:00	SPERRY, JOHN-ATTENDING	QUATTLEBAUM, T. G.-ATTENDI	LESTO, JANE-CLINIC-PG3		
:15	HEWETT, LEE-WC	TSURUTIS, VICTORI-RV	GREEN, IDA-CONF		
:30	... same...	DAWSON, ALLISON-WC	... same...		
:45	COOPER, KATHRINE-WC	... same...	... same...		
9:00	PERKINS, CHERYL-NICU-PG3	TOOL, SUSAN-GENERAL-PG3	BRANUM, SHERRY-ENDOC-PG2		
:15	DORCH, ADAM-BV EAR CHK	... same...	LESINGER, AUSTIN-WC		
:30	RILEY, KENDRA-SU	SANDERS, PATTY-WC	... same...		
:45	... same...	... same...	... same...		
9:00	EVANS, SARA-CARDIOL-PG2	GIEP, TUNG-ELECTIVE-PG2	CASTLES, GUY-CLINIC-PG1		
:15	BROWN, JONAS-WCF	CRAVEN, JESSIE-WC	REEVES, ROBERT-WC		
:30	BROWN, KIJANA-WC	... same...	... same...		
:45	... same...	... same...	... same...		
9:00	HEISEL, RAY-HEM/ONC-PG1	POWLER, LAURA-RV FU HOSP	Nurse		
:15	KING, CLIFTON-BV EAR CHK	WOLF, ALICIA-NURSERY-PG1	DELEE, GLORIA-BLOOD WORK		
:30	SMITH, ARLEY-SU	... same...	STRICKLAND, SEREN-SHOTS		
:45	WONG, JOWENE-RV F/U UTI	... same...	BOSC, ALICIA-URINALYSIS		

Sample appointment entry computer screen display. PG1 indicates first-year resident; PG2, second-year resident; and PG3, third-year resident. See Table for additional abbreviations.

Appointment Time Allocated for Various Types of Patient Problems					
Type of Appointment	Comment Abbreviations	Appointment Time, min			
		Resident Level			Attending Physician
		1	2	3	
Well check	WC	60	45	30	30
Well check for first of several in family	WCF	15	15	15	15
Brief visit	BV	15	15	15	15
Sick visit, return visit, and others	SV, RV	30	30	30	15
Medical conference	CONF	60	60	60	60

APPOINTMENT REMINDERS

Many published studies have shown that appointment reminders close to the time of the scheduled appointment reduced the number of missed appointments.¹¹ Efforts should be concentrated on those patients who are at highest risk of missing their appointments. It has been demonstrated that significant reductions in missed appointments are more likely to be achieved if appointment reminders are given to patients who have been scheduled more than 14 days before their appointment time.¹² Patients from lower socioeconomic groups are also at higher risk for missing appointments.¹¹

The scheduling system provides the automated printing of reminder postcards each week for mailing to patients who are scheduled for the following week. Cards are printed only for those appointments made more than 2 weeks before the scheduled date. These cards can be limited to those patients whose financial codes indicate that they fall into lower socioeconomic groups.

COMMENT

This system currently is being run on an IBM AT-compatible computer connected to seven terminals and four printers. These terminals are also used by office staff for billing and patient information systems, which are run simultaneously on the same computer. A simpler hardware setup consisting of a computer and one or two terminals and printers would be adequate for most outpatient residency practices. The use of several terminals allows patients to be given appointments by more than one individual and at several locations.

Printers are used with the scheduling system for making a daily list of patients and physicians scheduled for the next day's session in the clinic. This printout is helpful in locating charts for the scheduled patients before their arrival and for providing physicians and nursing staff a list of the day's patients. An "encounter form" is printed when each patient arrives. This form shows the patient's appointed and arrival times as well as demographic and billing information needed by the office staff. Space is present on the form for the physician to note the patient's diagnoses, the procedures involved in the visit, when the patient should return, and for what type

of visit. This information is used for making follow-up appointments as the patient leaves the office and for data entry into the billing system.

The automation of appointment reminders allows the office staff to quickly print postcards once each week. The criteria for printing these reminders allows them to be used in a cost-effective method by targeting those most likely to break their appointments. The effectiveness of these reminders in reducing the number of broken appointments is the subject of a current study.

Office staff have found the scheduling system simple and easy to use. With the previous manual scheduling system, busy personnel found it difficult to accurately and consistently schedule patients based on a resident's level of training and the patient's problem. Appointments were often scheduled too close together, leading to conflicts between the time allocated for one appointment and that needed for the next patient. When this happened, bottlenecks occurred in the flow of patients, leading to increased waiting and considerable patient and physician frustration. Other appointments were incorrectly made too far apart and resulted in increased physician idle time. The computerized system has provided improved patient flow while increasing satisfaction among office staff, patients, and physicians.

The benefits of the scheduling system that have been observed have led to plans for the installation of the complete scheduling system at another hospital. This new installation will allow patient and physician flow analyses and satisfaction studies to be performed both be-

fore and after installation to document in detail the improvements in patient care provided by the system. Information about the computer programs can be obtained on request.

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In Other AMA Journals

ARCHIVES OF SURGERY

Primary Repair Without Routine Gastrostomy Is the Treatment of Choice for Neonates With Esophageal Atresia and Tracheoesophageal Fistula

Donald B. Shaul, MD; Marshall Z. Schwartz, MD; Clifford C. Marr, MD; Kenneth R. T. Tyson, MD (*Arch Surg*. 1989;125:1188-1191)

Relative Carnitine Insufficiency in Children With Type I Diabetes Mellitus

Susan C. Winter, MD; Mary Simon, MD; Elinor M. Zorn, MD; Stefan Szabo-Aczel, MD; W. Hugh Vance, PhD; Timothy O'Hara; Linda Higashi

● **Recognizing the similarity of type I diabetes mellitus to inborn errors of metabolism that have responded to carnitine therapy, we initiated a study of 54 children with type I diabetes mellitus. Examining a fasting blood sample for levels of carnitine, glucose, and glycosylated hemoglobin A_{1c}, and a urine sample for levels of ketones and glucose, we found 13 children were deficient of free carnitine (<20 $\mu\text{mol/L}$) and 30 had elevated acyl carnitine levels (>11 $\mu\text{mol/L}$). Statistical tests confirmed a significant difference between the diabetic population and normal population for reduced free carnitine, elevated acyl carnitine, and an elevated ratio of acyl carnitine to free carnitine. Also, a significant correlation was found between the levels of urine glucose and ketones and the level of acyl carnitine. Our data indicate that carnitine deficiency and relative insufficiency may be an overlooked component in the management of diabetes. (AJDC. 1989;143:1337-1339)**

Carnitine is a naturally occurring substance and a necessary cofactor in fatty acid metabolism. Specifically, carnitine functions as a cofactor of carnitine translocase, acyl carnitine transferase I, and acyl carnitine transferase II, which act to convert free long-chain fatty acids to acyl carnitines and transport them into the mitochondrial matrix (Figure). β -Oxidation of fatty acids precedes entry of the two carbon moieties into the Krebs cycle where production of adenosine triphosphate occurs. Carnitine also transports shortened acyl coenzyme A (CoA) compounds from peroxisomes to mitochondria. Through these activities, carnitine regulates the cytosolic and mitochondrial acyl CoA/free CoA ratio. Availability of free CoA is vital for maintaining adequate adenosine triphosphate production.^{1,2}

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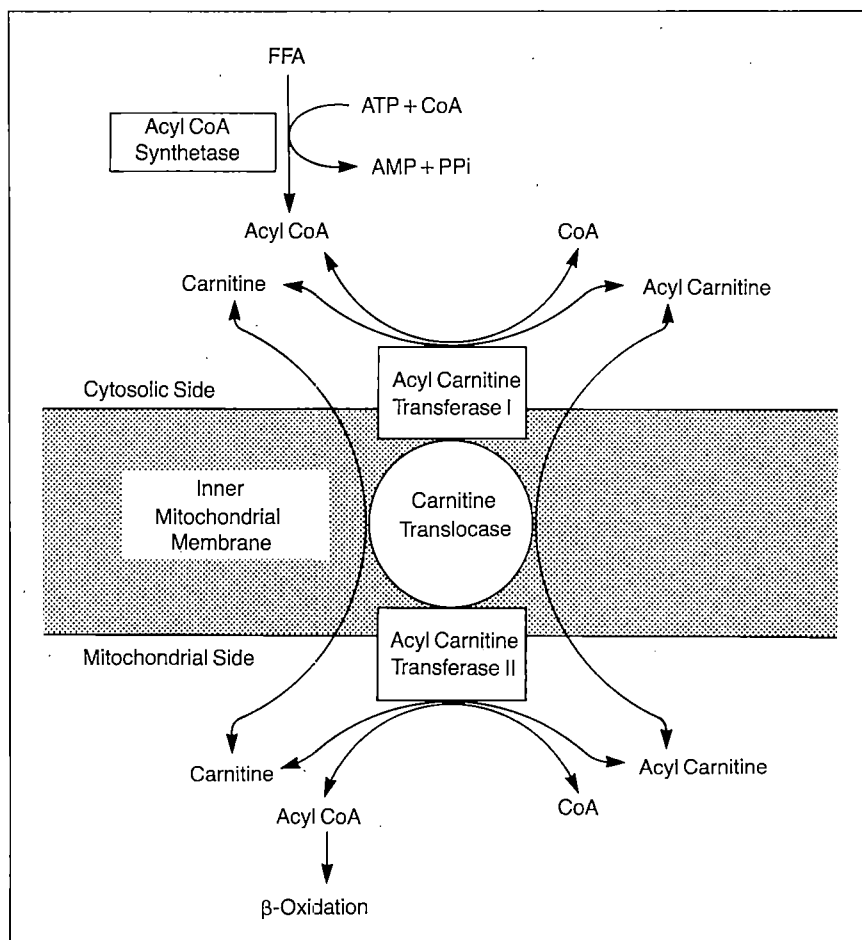
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Carnitine is synthesized by the body, with the final step of synthesis occurring in the liver and kidney. Dietary sources, such as red meat and dairy products, supply an important portion of the body's carnitine stores. No pathways of degradation have been identified, with the main mechanism of loss being excretion via the urine.^{1,2} Preferential reabsorption of free carnitine is an active process with a well-defined threshold that effectively regulates plasma free carnitine levels in normal conditions, while the majority of esterified carnitine (acyl carnitine) is excret-

ed via the urine.³ Therefore, prolonged elevation of carnitine esters, such as occurs in organic acidopathies, may cause a depletion of carnitine stores. In addition, we postulate that the moment-to-moment availability of free CoA depends on free carnitine availability. A shift toward esterified CoA results in an increase in the ratio of esterified carnitine vs free carnitine, a so-called relative carnitine insufficiency, which leads to decreased energy production. Such a shift should be reversible if additional free carnitine is supplied.

Carnitine deficiency states have been



Diagrammatic representation of the function of carnitine at the inner mitochondrial membrane. All transfers at the membrane are reversible, and inadequate carnitine levels may decrease transfer of free fatty acids (FFA) into the mitochondrion as well as transfer of acyl compounds from the mitochondrion. ATP indicates adenosine triphosphate; AMP, adenosine monophosphate; CoA, coenzyme A; and PPI, inorganic phosphate.

described, and symptoms include lipid storage myopathy, cardiomyopathy, progressive muscle weakness, hepatic encephalopathy, nonketotic hypoglycemia, failure to thrive, and recurrent infections. Treatment by dietary supplementation of carnitine has been successful, in the majority of cases, in ameliorating or resolving the problems associated with low levels of free carnitine.⁴⁻⁷

Early reports by Bohmer et al¹⁸ in 1974 and by Cederblad et al¹⁹ in 1977 described no significant difference in tissue and plasma carnitine levels in diabetic patients as compared with control subjects. Later, de Palo et al²⁰ and Cederblad et al,²¹ who studied 52 patients between the ages of 8 and 20 years, both reported significantly reduced levels of total and plasma free carnitine. Cederblad et al²¹ also reported significantly increased levels of acyl carnitines in their patients. In addition, several studies have reported decreased levels of free carnitine and increased levels of acyl carnitine during diabetic ketosis.²²⁻²⁵

The metabolic dysfunction in diabetes bears a striking similarity to many of the inborn errors of metabolism that have responded well to carnitine supplementation. Diabetes, when it is poorly controlled, increases demand on carnitine stores due to the increased oxidation of fats and degradation of protein, with production of acyl CoA compounds requiring carnitine for clearance. We, therefore, hypothesize that diabetic children, specifically those whose disease is poorly controlled, have an increased incidence of reduced plasma free carnitine, elevated esterified carnitine, and altered acylated-to-free carnitine ratio, a relative carnitine insufficiency, when compared with a non-diabetic population. Also, we expect the four indicators of control of diabetes that we examine—glycosylated hemoglobin A_{1c} (HbA_{1c}), blood glucose, urine glucose, and ketonuria—will correlate with acyl carnitine levels.

PATIENTS AND METHODS

Fifty-four children with type I diabetes mellitus were included in the study. All patients attended a diabetes camp at Bearskin Meadows in the Sierra-Nevada Mountains in central California. Approval for the study was obtained from the Board of Trustees governing the camp, and all patients participated voluntarily with consent forms being

obtained from each patient or the patient's legal guardian.

A urine sample was collected, and a single blood sample was obtained by venipuncture in the morning prior to receiving insulin or eating. Blood was divided into aliquots and analyzed on site for glucose with a test strip utilizing the glucose oxidase-peroxidase reaction (Chemstrip, Boeringer Mannheim) or frozen on dry ice for shipment to laboratories for determination of carnitine levels using the modified radiometric method of Parvin and Pande²⁷ (Metabolic Analysis Laboratory, Madison, Wis) and HbA_{1c} (SmithKline & French Laboratory, Fresno, Calif). Urine was analyzed for glucose and ketones by dipstick.

All children were healthy when tested and displayed normal activity. Age, ethnic origin, diet, date of onset of diabetes, height, and weight were recorded. Control data were derived by analyzing samples taken from 20 randomly selected patients, of similar age and normal health, after random blood samples were drawn at Valley Children's Hospital, Fresno, Calif.

Data analysis was accomplished using the Student *t* test, χ^2 analysis, and multiple regression.

RESULTS

Of the 54 children studied for correlation between control of diabetes and plasma carnitine levels, 31 were boys and 23 were girls; their ages ranged from 7 to 18 years with a mean (\pm SD) of 11.9 ± 2.8 years. The group included 46 white children, 4 Hispanic, 2 Asian, 1 black, and 1 American Indian. The age of onset of diabetes was between 0.4 and 15 years with a mean (\pm SD) of 7.2 ± 3.4 years. Personal histories revealed normal diets with no vegetarians and no medications other than insulin being taken.

Thirteen patients had a plasma free carnitine level we define as deficient—less than $20 \mu\text{mol/L}$, or 2 SDs below the mean of $39 \pm 10 \mu\text{mol/L}$. The number of girls as compared with the number of boys with plasma free carnitine deficiency was significant at the $P < .01$ level, with 10 of the 13 carnitine-deficient patients being girls as compared with 13 of the 41 nondeficient patients being girls. The length of time affected with diabetes was not significantly different for the carnitine-deficient and nondeficient groups, nor did age seem to be a factor since the mean age of the carnitine-deficient group (12.7 ± 3.7 years) was not significantly different from the population as a whole.

When comparing levels of free and esterified carnitine and the ratios of the esterified to free levels of our patient population with values derived from 20 control subjects of similar age and sex distribution, the patient population was significantly different, with $P < .001$ for free and esterified carnitine and the ratio of esterified to free carnitine (Table 1).

When all indicators of diabetes control were examined (levels of blood glucose, urine ketones, urine glucose, and HbA_{1c}), 43 of the 54 patients had at least one value indicating poor control of diabetes, and 11 had all values within normal levels (Table 2).

Plasma esterified carnitine values beyond the limit of normal ($11 \mu\text{mol/L}$) were found in 30 of 54 patients (Table 2). When the patients with abnormal values for at least one of the control indicators were examined for correlation with elevated levels of esterified carnitine, we found that the urine glucose level demonstrated significant correlation at $P < .03$, and urine ketone levels dem-

Table 1.—Plasma Carnitine Levels*

	Free Carnitine, $\mu\text{mol/L}$	Esterified Carnitine, $\mu\text{mol/L}$	Ratio
Patients (n=54)	24.7 ± 6.0	12.5 ± 6.0	0.52 ± 0.31
Controls (n=20)	35.0 ± 7.4	9.3 ± 5.0	0.29 ± 0.21

*The patient population differed from the control population with $P < .001$ for all categories. All values are mean \pm SD. The ratio is that of esterified to free carnitine.

Table 2.—Incidence of Values Indicating Poor Control of Diabetes in Patients With Elevated and Normal Esters*

Characteristic	Elevated Esters (n=30)	Normal Esters (n=24)	All Patients (n=54)
Glycosylated hemoglobin A _{1c}	5	9	14
Hyperglycemia (glucose level >7.8 mmol/L)	12	7	19
Ketonuria	12	3	15
Glycosuria	23	10	33
All values normal	4	7	11

*Incidence of ketonuria and glycosuria demonstrated significant correlation ($P < .03$ and $P < .05$, respectively) with elevated esters.

onstrated significant correlation at $P < .05$. The levels of HbA_{1c} and blood glucose did not correlate with elevated levels of esterified carnitine. However, the mean level of blood glucose (7.7 ± 3.0 mmol/L) of the 30 patients with abnormally elevated esterified carnitine was significantly different from the mean level of blood glucose of the patients with normal ester levels (5.9 ± 1.8 mmol/L) at the $P < .05$ level.

COMMENT

In our population of 54 pediatric patients with type I diabetes mellitus, a statistically significant group, 24% (13/54), were deficient of plasma free carnitine. This agrees with numerous previously published observations.^{22,26} Of interest was the statistically significant number of carnitine-deficient girls (10 of 13) recorded. An explanation we offer is that the age of the girls (mean, 13.5 years) coincides with the onset of menses, and this complex event may, in some subtle way, influence carnitine levels. Certainly we know of no studies that have been directed specifically at this issue.

As we expected, the free carnitine and esterified carnitine levels as well as the esterified/free ratio of the diabetic population were significantly different from those of the normal population ($P < .001$). This is a reflection of recurrent episodes of ketosis with a concomitant need to clear acyl CoA derivatives in the diabetic patient.

When we attempted to examine degree of control of diabetes by correlating HbA_{1c}, ketonuria, glucosuria, or blood glucose levels with esterified carnitine levels, the results did not fit our hypothesis. The elevation of urine glucose and ketone levels correlated significantly with carnitine esters, but HbA_{1c} and blood glucose levels did not (Table 2). Since the amount of esterified carnitine in the blood changes on a moment-to-moment basis and reflects rapid intracellular changes in acyl CoA production, perhaps these findings suggest that acute swings in metabolism occurred throughout the night and were reflected in urine glucose and ketone values we found by collecting a sample the following morning. If such swings do not last for extended periods, HbA_{1c} would likely not be elevated, but repeated short time course episodes of

such swings would result in carnitine depletion. The lack of correlation with elevated blood glucose levels may simply be due to the fact that we did not obtain a continuous blood glucose monitoring prior to obtaining carnitine levels. Indeed, hyperglycemia may have occurred throughout the night and remained undetected in the morning sample.

In our opinion, the most sensitive indicator of carnitine insufficiency is the ratio of esterified carnitine to free carnitine, which increases during insufficiency states. During diabetic ketosis, relative carnitine insufficiency can occur due to the build-up of acyl CoA derivatives.^{21,26} This insufficiency will result first in decreased adenosine triphosphate production and, if sustained, will eventually result in outright deficiency of free carnitine as a result of urinary excretion of esterified carnitine.⁸ Carnitine deficiency, therefore, can result from repeated bouts of ketosis. Due to decreased fatty acid transport under conditions of carnitine deficiency, ketosis no longer occurs, with the result being conditions favoring the clinical phenomenon known as nonketotic hypoglycemia.

We see our findings as preliminary but suggesting that relative carnitine insufficiency may be an overlooked and treatable component in the management of diabetes. Further controlled studies on large populations of diabetic patients receiving carnitine supplements are warranted.

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The Board of Directors and personnel at the Bearskin Meadows Camp, the Valley Children's Hospital Laboratory, and the University of California, San Francisco, Medical Library staff cooperated in this study, and Lawrence Linn provided assistance with the statistical analysis.

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Serum Phosphate Concentration

Effect on Serum Ionized Calcium Concentration In Vitro

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• We examined the effects of variations of serum phosphate levels on serum ionized calcium concentrations in vitro. A single donor serum sample was divided into 25 aliquots stored in tubes sealed with carbon dioxide and divided into 5 subsets of tubes. The pH was altered in 4 of the 5 subsets by adding various concentrations of hydrochloric acid or sodium hydroxide. The pH levels studied ranged from 7.09 to 7.63. The phosphate concentration was altered in each subset by adding various concentrations of a phosphate buffer. The phosphate concentrations studied ranged between 0.81 and 3.58 mmol/L. There was an inverse relationship between ionized calcium and phosphate at all pH levels studied. The ionized calcium concentration correlated inversely with pH. We suggest that in addition to factors well known to influence serum ionized calcium concentration (such as protein, bicarbonate, and pH values), serum phosphate concentration also plays an important role.

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Total serum calcium is present in three forms: ionized, complex, and protein bound. Ionized calcium is the active form and consists of 45% to 50% of total calcium. Complex calcium (5% to 10% of total calcium) is that calcium bound to major anions such as lactate, citrate, sulfate, bicarbonate, and phosphate. The remaining 40% to 45% of total calcium is protein bound. Several variables may affect the balance among these three forms. The effects of changes in blood pH and serum protein, bicarbonate, and magnesium concentrations have been thoroughly studied and

reported.¹⁻⁵ There are no studies of the direct effect of the serum phosphate level on serum ionized calcium concentrations, though from indirect studies it is generally believed that high serum phosphate levels may decrease serum ionized calcium concentrations.⁶ Since there might be rather wide physiologic and nonphysiologic variations of serum phosphate concentrations, particularly in childhood, we examined the effects of varying phosphate concentrations on ionized calcium concentrations in vitro. We hypothesized that, within the range of clinically encountered pH, an increasing serum phosphate concentration would lead to a decreasing ionized calcium concentration.

METHODS

A buffer solution of phosphate was prepared using 1 mol/L of monosodium acid phosphate with 1 mol/L of monobasic potassium phosphate added slowly until a pH of 7.4 was obtained. The pH was checked with a pH probe (Metrohm/Brinkmann, Westbury, NY). The 1-mol/L buffer solution was then diluted to a 0.03-mol/L solution, and its measured phosphate content was 0.81 mmol/L; the pH of the diluted solution was 7.4.

One of us (M.L.) provided the serum for study (pH 7.35); it was divided into 25 aliquots of 250 μ L each. Serum was obtained and stored in tubes sealed with 5% carbon dioxide (partial pressure of carbon dioxide in exhaled air to stabilize pH) and divided into 5 subsets of 5 tubes each. Alterations in pH were made in 4 of the 5 subsets by adding the following: 8 μ L of 0.125N hydrochloric acid (leading to a serum pH of 7.28); 17 μ L of 0.125N hydrochloric acid (leading to a serum pH of 7.09); 10 μ L of 0.125N sodium hydroxide (leading to a pH of 7.51); and 20 μ L of 0.125N sodium hydroxide (leading to a pH of 7.63). Alterations in phosphate concentration were made in each subset by adding 0, 5, 10, 15, or 20 μ L of the 0.03-mol/L phosphate buffer. Deionized water was added to each tube to reach a total volume of 290 μ L. Sam-

ples were mixed well and allowed to equilibrate overnight at 4°C.

Ionized calcium concentration and pH were assayed the following day with an ion-selective electrode (Radiometer ICA1, Radiometer Laboratories, Copenhagen, Denmark). This electrode warms the sample to 37°C (body temperature) for subsequent analysis of both pH and ionized calcium. Results of ionized calcium concentration determinations are given for the actual pH and are corrected for a pH of 7.40. The SE of measurement for this electrode is 0.012 mmol/L. Our normal range for adults is 1.20 to 1.29 mmol/L, with a coefficient of variation of 2.63%.

The serum phosphate concentration was measured (ABA 100 Analyzer, Abbott Laboratories, South Pasadena, Calif). Our normal range for adults is 0.62 to 1.17 mmol/L, with a coefficient of variation of 1.8% to 2.8%.

Statistical analysis was done by linear regression and multiple regression analyses, using the SAS package (SAS Institute, Cary, NC). $P < .05$ was considered significant.

RESULTS

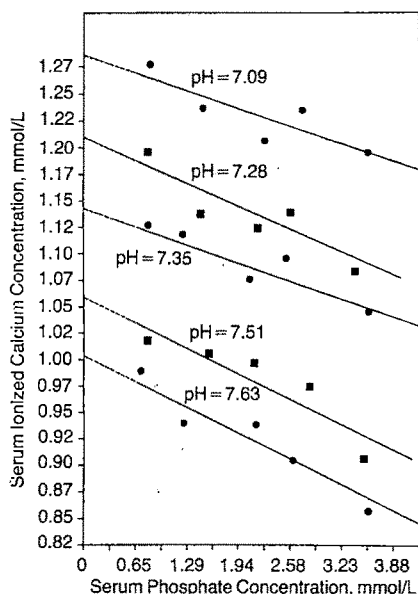
The pH was used as a categorical variable for the five groups. In the Figure, we show the regression of ionized calcium concentrations on phosphate concentration at each pH level. An inverse relationship between ionized calcium concentration and phosphate concentration is noted. At all pH levels studied, the effect of phosphate concentration on ionized calcium concentration was similar: the observed slopes did not differ significantly from the theoretical common slope of -0.042 , indicating no significant deviation from parallelism of these five regression lines.

The five intercepts of ionized calcium in relation to phosphate (Figure) differed significantly from each other ($P < .05$), pointing out the effect of pH on the ionized calcium concentration. In multiple regression analysis, the ionized calcium concentration was inverse-

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Plot of serum ionized calcium concentrations in relation to serum phosphate concentrations at various pH levels: top slope (circles), pH=7.09, $r = -.8378$, $P < .001$; second slope (boxes), pH=7.28, $r = -.8981$, $P < .001$; third slope (circles), pH=7.35, $r = -.9357$, $P < .001$; fourth slope (boxes), pH=7.51, $r = -.9027$, $P < .001$; and bottom slope (circles), pH=7.63, $r = -.9403$, $P < .001$.

ly correlated with pH ($R^2 = .9842$, $P < .01$); there was no significant interaction between phosphate concentration and pH.

COMMENT

From the results of this investigation, the ionized calcium concentration in vitro appears to be inversely related to both phosphate concentration and pH. The effect of increased phosphate concentration on ionized calcium concentration is similar at various pH levels between 7.09 to 7.63.

Previous studies have shown that increases in serum phosphate concentrations result in decreases in ultrafilterable calcium.⁶ However, ultrafilterable

calcium does not reflect exactly ionized calcium, since it includes both ionized calcium and complex calcium. Now, with recent technological advances in ion-selective electrodes, it is possible to measure directly, accurately, and consistently the concentration of serum ionized calcium.⁷⁻⁹

The effect of pH on serum ionized calcium concentration has been well studied in the past, and it is likely that this effect is due to the competition of hydrogen ions with ionized calcium for proteins.^{6,10}

The results of our study support the hypothesis that phosphate may bind to ionized calcium to form a complex form of calcium. The phosphate concentrations studied are frequently observed in children. Based on this in vitro study, an increase of 0.65 mmol/L of serum phosphate concentration may be associated with a decrease close to 0.25 mmol/L of serum ionized calcium. Thus, the effect on ionized calcium concentration may be clinically significant.

A limitation to our study is that it may not be possible to extrapolate from it directly to in vivo situations. In vivo, multiple other interactions may occur; a decrease in ionized calcium concentration leads to compensatory mechanisms, such as an increase in parathyroid hormone secretion and decreased calcitonin production, that may have significant effects on major target organs such as bone, kidney, and intestine.¹¹ In addition, our titration study used a blood sample obtained from a single donor. It is theoretically possible that results using serum with different protein or calcium salt concentrations would lead to quantitatively different results, though the general relationship between serum ionized calcium and phosphate concentrations should qualitatively be the same.

Thus, in addition to factors well known to influence ionized calcium con-

centration (such as protein, bicarbonate, and pH levels), serum phosphate concentration also may play an important role. Since measurement of serum ionized calcium concentration has become a reliable and clinically useful technique,⁷⁻⁹ it may be logical to substitute direct ionized calcium for total calcium measurements in clinical practice.

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Richard Ross, PhD, advised on the study; William Hull, Donna Buckley, and Victoria Neumann provided technical assistance; Jane Holroyde, statistical help; and Renee McKenzie, typed the manuscript.

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In Other AMA Journals

JAMA

The Cost of Clinical Trials

R. H. Fletcher (JAMA. 1989;262:1842)

Serum Alkaline Phosphatase and Serum Zinc Concentrations in Preterm Infants With Rickets and Fractures

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• This study aimed to determine the longitudinal changes in serum zinc concentrations and the relationship between serum alkaline phosphatase (AP) activity and serum zinc concentrations in small preterm infants. The total serum AP and serum zinc concentrations were determined serially at 3, 6, 9, and 12 months in 72 infants with mean (\pm SEM) birth weights of 1000 ± 29 g and gestational ages of 28.6 ± 0.3 weeks. Twenty-four of 72 infants had radiographic evidence of rickets and/or fractures (R/F). In infants with R/F, group mean (\pm SEM) serum AP (371 ± 42 U/L) and serum zinc (12.5 ± 1.0 μ mol/L) concentrations were significantly higher at 3 months compared with infants in the non-R/F group (193 ± 12 U/L and 9.6 ± 0.3 μ mol/L, respectively). During the study, the serum AP concentrations decreased, and the serum zinc concentrations increased; both stabilized after 6 months. The serum AP concentrations were not related to the serum zinc concentrations. We speculate that in preterm infants, an increased bone turnover and a release of tissue (bone) zinc may contribute to the higher group mean serum AP and serum zinc concentrations at the time of diagnoses in infants with R/F compared with those infants without R/F.

(AJDC. 1989;143:1342-1345)

Alkaline phosphatase (AP) is a zinc-dependent¹ enzyme that is secreted by osteoblasts²⁻⁴, and serum AP activity appears to relate to the serum zinc concentration^{5,6} and zinc therapy.^{6,7} In normal pediatric populations, 80% to 90% of the total serum AP activity is of bone

origin.^{4,8-10} Serum AP activities are elevated in states of increased bone turnover, eg, during periods of rapid growth in infants and adolescents^{8,11,12} and in patients with rickets and/or fractures (R/F).^{2,3-12} However, serum AP activity may not be elevated in all infants with R/F,¹³⁻¹⁶ and it is not known whether the low serum AP activity in these circumstances is associated with low serum zinc concentrations. This study aimed to determine the longitudinal changes in the serum AP activity and serum zinc concentrations in small preterm infants and in the relationship between these two serum variables. We also tested the hypotheses that in infants with R/F, the serum AP activity is increased, and a low serum AP activity is associated with a low serum zinc concentration.

PATIENTS AND METHODS

Seventy-two infants with mean (\pm SEM) birth weights of 1000 ± 29 g (range, 420 to 1500 g) and gestational ages of 28.6 ± 0.3 weeks (range, 23 to 36 weeks) who had serial radiographic documentation for the presence ($n=24$) or absence ($n=48$) of skeletal abnormalities of R/F at 3-month intervals during the first year were the subjects of the present study. Radiographic abnormalities were found in 7 infants with fractures, 6 infants with rickets, and 11 infants with R/F. All active skeletal abnormalities occurred before the 6-month screening radiograph, and all these abnormalities in the infants with R/F were healed by 12 months. Details of the clinical and radiographic changes have been presented elsewhere.^{17,18} None of the investigators knew the skeletal radiographic status of the infants before their enrollment in the study. All aspects of clinical management for each infant were made by the same group of physicians during each infant's hospitalization and by the physician of the parents' choice after the infant's discharge from the hospital.

Blood collection and serum separation employed the use of stainless steel needles or butterfly needles and disposable plastic sy-

ringes. Blood and serum samples were stored in polypropylene containers. Needles, syringes, and polypropylene containers were checked at random and were free of detectable zinc. Nonfasting blood samples were collected from each infant at the mean postnatal ages of 3, 6, 9, and 12 months, ie, the same study points as the clinical and radiographic assessments. The conditions of all the infants were clinically stable at the time of assessment, and no visible hemolysis was noted in any serum samples. Serum samples were stored at -70°C and measured for AP and zinc in batches by technicians with no knowledge of the radiographic status of each infant.

The serum AP value was measured by the method of Wilkinson et al,¹⁹ by using a centrifugal analyzer. The serum AP values for normal adults range from 18 to 72 U/L at 30°C . The interassay coefficient of variation was 3.5%.

The serum zinc value was measured by using flame atomic absorption spectrophotometry with a modified spectrophotometer (Perkin-Elmer 503, Perkin-Elmer Corp, Norwalk, Conn) that was fitted with a deuterium arc background correction and an auto-sampling system (AS3). For analysis, duplicate samples of 150- μ L aliquots of serum were transferred to small circular quartz dishes for overnight ashing in a low-temperature asher (LFE Corp, Waltham, Mass). The ash samples were dissolved with 150 μ L of 0.1N hydrochloride. A 100- μ L aliquot of the dissolved ash was diluted with 500 μ L of 6% butanol in 0.1N hydrochloric acid.^{20,21} Standards also were made up in 6% butanol in 0.1N hydrochloric acid. The interassay coefficient of variation was 1.7%. The detection limit for this assay was 0.6 μ mol/L. The normal adult reference range is from 9.2 to 15.4 μ mol/L (1 μ g/dL = 0.154 μ mol/L). The value obtained for the National Bureau of Standards bovine liver (certified value = 130 ± 13 μ g [mean \pm SD] of zinc per gram of dry weight), by using the same analytical techniques, was 129 ± 3 μ g of zinc per gram of dry weight.

The nutrient intakes during infancy¹⁸ were similar between the groups, except that infants with R/F received parenteral nutrition

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Changes in Weight, Length, and Serum Biochemical Measurements in VLBW Infants With and Without R/F During Infancy*

	Group, Mean \pm SEM†							
	A (n=21)	B (n=40)	A (n=19)	B (n=40)	A (n=17)	B (n=41)	A (n=14)	B (n=34)
Postnatal age, d	98 \pm 1.8		184 \pm 1.7		277 \pm 1.7		371 \pm 2.2	
Independent variables								
Weight, g	2359 \pm 181	2965 \pm 128	4018 \pm 287	5159 \pm 166	4988 \pm 242	6645 \pm 209	6830 \pm 314	7859 \pm 239
Length, cm	45.6 \pm 1.3	48.0 \pm 0.6	52.5 \pm 1.6	56.9 \pm 0.6	59.7 \pm 1.2	64.0 \pm 0.6	65.9 \pm 1.2	69.1 \pm 0.6
Dependent variables								
Serum alkaline phosphatase, U/L at 30°C	371 \pm 42‡ (21)	193 \pm 12 (40)	201 \pm 27‡ (19)	152 \pm 10 (40)	121 \pm 10 (17)	120 \pm 6 (41)	109 \pm 10 (14)	134 \pm 17 (34)
Serum zinc, μ mol/L	12.5 \pm 1.0§ (14)	9.6 \pm 0.3 (31)	13.7 \pm 0.9§ (13)	11.9 \pm 0.4 (26)	13.6 \pm 0.7 (16)	12.5 \pm 0.4 (27)	13.3 \pm 0.6§ (11)	12.3 \pm 0.3 (26)

*VLBW indicates very-low-birth-weight; R/F, rickets and/or fractures; and numbers in parentheses, number of samples assayed.

†Radiographic R/F in VLBW infants: A = present and B = absent.

‡Initial values were higher and rate of decline was faster in infants with R/F ($P < .001$, respectively, by random coefficient regression analyses). No significant difference between groups after 6 months.

§Initial values were higher and rate of increase was slower in infants with R/F ($P < .001$, respectively, by random coefficient regression analyses). No significant difference between groups at 9 months.

for longer periods (40 \pm 11 days vs 16 \pm 3 days [mean \pm SEM], $P < .001$) and they received preterm infant formula for longer periods (23 \pm 7 days vs 4 \pm 1 days [mean \pm SEM], $P < .001$). Standard parenteral nutrition delivers 300 μ g of elemental zinc per kilogram per day. Other components of standard parenteral nutrition were used as previously described.²²

At one of the blood sampling times, two infants received total parenteral nutrition for temporary feeding intolerance. All infants received enteral feedings when the blood samples were taken at other times. Enteral nutrients included mother's milk or 2814 kJ/L of standard cow's milk formula. Mother's milk was used for 9 of 24 infants in the R/F group and for 22 of 48 infants in the non-R/F group. Vitamin D-fortified whole cow's milk was introduced in 4 infants (1 in the R/F group) by 9 months and in 15 infants (4 in the R/F group) by 12 months. An increased enteral zinc intake in the form of preterm infant formula (Similac Special Care, Ross Laboratories, Columbus, Ohio) or powdered human milk fortifier (Mead Johnson & Co, Evansville, Ind) was given to 30 infants (17 in the R/F group) for 1 to 183 days (median, 26 days). Soy formula (Isomil, Ross Laboratories) was given to 3 infants (1 in the R/F group) for more than 3 months, and it was given to another 6 infants (4 in the R/F group) intermittently as clinically indicated. Protein hydrolysate formula (Pregestimil, Mead Johnson Co) was given to 6 infants (1 in the R/F group) for 6 months or greater.

This study was approved by the Review Board for Human Investigation, and written informed consent was obtained from a parent of each subject.

STATISTICAL METHODS

For replicated measurements, the natural logarithm of each serum variable was used to normalize the statistical distributions. In addition, the postnatal age of each infant at measurement was transformed to its natural logarithm to allow for deviations from linearity in the changes of serum variables over time. The serial changes with age for each variable were estimated for each infant by random coefficient regression analyses.^{23,24}

The serial changes of each serum variable in infants with R/F were compared with those in infants without R/F in a linear regression model, controlling for any significant potential covariates (confounding variables). The strategy of backward elimination was used to select the potential covariates that significantly affected the serial changes in the serum AP or serum zinc concentrations. Only the significant potential covariates were retained in the statistical model in the final analysis. The covariates used were gender, birth weight, gestational age, body weight, and length at each study, since these factors have been reported to affect the serum AP^{8,9,11,25} or serum zinc^{26,27} concentrations. The amount of zinc delivered from parenteral nutrition, preterm infant formula, and powdered human milk fortifier is greater than that from human milk or standard formula²⁸; thus, the durations for which these nutrients were received by the infants also were entered as potential covariates in the statistical model.

Statistical analyses were performed by using the CLINFO program of the National Institutes of Health, at the General Clinical Research Center of the University of Cincinnati (Ohio), and the Computer Center main-

frame computer (Amdahl 5880) at the University of Cincinnati. A P value of .05 was used to judge the significance of each estimated parameter in all statistical tests.

RESULTS

The serial changes in the serum AP and serum zinc concentrations are shown in the Table. Owing to the blood volume limitations, the serum AP value was measured in 72 infants (24 with R/F), and the serum zinc value was measured in 49 infants (17 with R/F). The serum zinc measurements were available only for infants who were receiving enteral feedings; 3 infants with R/F and 1 infant without R/F were receiving a premature infant formula on the day of blood sampling for a total of four and one occasions, respectively. The nutrient intake was otherwise similar between the groups.

For the serum AP values, body weight was the only significant covariate ($P < .001$). The mean initial serum AP values were elevated in both groups compared with the adult norms and were significantly higher in the R/F group. The serial serum AP values decreased in both groups, but the rate of decrease in the serum AP values was significantly greater in infants with R/F ($P < .001$). There was no significant difference in the serum AP values between the groups after the second measurement at 6 months. One infant with persistent cholestatic jaundice, presumably from the prolonged use of par-

enteral nutrition, had one simultaneous serum AP and serum zinc measurement. The values were 152 U/L and 13.9 $\mu\text{mol/L}$, respectively.

For the serum zinc concentrations, none of the potential covariates that were entered into the regression models were statistically significant. The initial serum zinc concentrations were significantly higher in the R/F group. The serial serum zinc concentrations increased in both groups, but the rate of increase in the serum zinc concentrations was significantly greater in infants without R/F ($P < .001$). The difference in the mean serum zinc concentrations between the groups became smaller with increasing age.

There was a weak positive correlation ($r = .23$) between the estimated serial changes in serum AP and serum zinc concentrations that was not statistically significant ($P = .18$).

COMMENT

The normal range of serum AP concentrations for very-low-birth-weight infants has not been well defined²⁹ because most reports have included few subjects with simultaneous serum AP data and radiographic documentation of skeletal status. To our knowledge, this is the only study with serial radiographic documentation through the active phase to complete healing of the skeletal lesions in very-low-birth-weight infants with simultaneous serum AP and serum zinc measurements.

The serum AP activity, expressed as a proportion of the adult reference range, minimizes the difficulty in interpreting data from the methodological differences in the serum AP measurement.^{12,29} In the present study, the group mean serum AP activity at the time of the diagnosis of R/F was approximately 5.2 times the upper reference range for normal adults in our laboratory and was similar to that reported by others.¹² This was significantly higher than the group mean serum AP activity in the non-R/F group and was consistent with a further increase in bone turnover from R/F that was superimposed on the rapid growth of these small preterm infants. The decline in the serum AP activities with increasing age and the similarity of serum AP activities between the groups during the second half of

infancy were consistent with radiographic healing of R/F. However, the serum AP activity at 1 year in both groups remained higher than the adult reference range by 1.5- to 1.9-fold. This is consistent with the continued skeletal growth and bone mineralization in these infants.

It has been reported that an absence of an increased serum AP activity is associated with hypozincemia and hypomagnesemia,⁶ and infants with chronic diarrhea who are receiving inadequate zinc replacement may have low serum AP and serum zinc concentrations.⁶ The elevation of serum zinc concentrations on zinc replacement is associated with an elevation of the serum AP activity.^{6,7} In infants with rickets, there has been no documentation as to whether a low serum zinc concentration occurs in association with a normal or low serum AP activity.¹²⁻¹⁶ In the present study, absolute concentrations and changes in the serum AP values were not significantly correlated with the serum zinc concentrations; thus, the low serum AP activity in some infants with R/F could not be accounted for by low serum zinc concentrations. However, this study was not designed to measure zinc status, and we cannot rule out the possibility of a relatively zinc-deficient state in some of our infants who underwent studies.

It is known that the major source of the total serum AP activity in infants and children is of bone origin.^{4,8-10} All but two patients in this study had not received parenteral nutrition for many weeks before the first blood sampling, which may account for the low rate of persistent jaundice. Hepatic AP, therefore, is unlikely to account for a large proportion of the total serum AP activity. The activities of all isozymes of AP are zinc dependent and should not affect the determination of the relationship between the total serum AP activities and the serum zinc concentrations in this study.

The serum zinc concentrations, on initial sampling at 3 months, were higher in infants with R/F. It is theoretically possible that a greater zinc intake from parenteral nutrition and zinc-fortified milk intake before the blood sampling may have accounted for the higher serum zinc concentrations in the R/F group. However, an increased zinc in-

take in infants from both groups were controlled in our statistical analyses and were demonstrated to have no significant influence on the serum zinc concentrations. The release of tissue (bone) zinc from the increased bone turnover in rapidly growing infants, particularly those with R/F, may be responsible for the higher serum zinc concentrations. This finding is supported by the report of higher serum concentrations of 1,25-dihydroxyvitamin D in small preterm infants with R/F compared with those infants without R/F³⁰ which presumably results in increased osteoblastic activity and bone turn-over.^{3,31}

The serum zinc concentrations in our infants who underwent studies increased with increasing postnatal age. This finding is consistent with the changes in the serum zinc concentrations for term infants.³² The concentrations of serum zinc in our infants who underwent studies also were similar to those reported for term infants.^{32,33} Consistent with the healing of R/F and presumably a decreased release of tissue zinc, in particular that from bone, the serum zinc concentrations were similar in both groups after 6 months.

In conclusion, we have demonstrated that group mean serum AP and serum zinc concentrations are higher in infants at the time of the diagnosis of R/F. There were no correlations for the serum AP and serum zinc concentrations. We suggest that an increased serum AP value is consistent with an increased bone turnover. The higher the serum zinc values in infants with R/F at 3 and 6 months presumably are consistent with the release of tissue zinc from the increased bone turnover. In the present study, with increasing postnatal age and healing of R/F, serum AP and serum zinc concentrations became stabilized and were similar in very-low-birth-weight infants, regardless of their previous radiographic status with respect to R/F.

This study was supported by grants 5R01 HD 18505, RR123, and RR68 (CLINFO) and by Clinical Associate Physician Award 3M01 RR 00123-21S1 (Dr Koo) from the National Institutes of Health, Bethesda, Md, by grant 5R22AM12432 from the National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Md, and by grant RR69 from the National Institutes of Health.

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CORRECTION

Incorrect Order of Authors' Names.—In the letter to the editor entitled "Fructose-1,6-diphosphatase Deficiency: A 20-Year Follow-up," published in the February 1989 issue of *AJDC* (1989;143:140-142), the authors' names in the signature on page 141 were listed in the incorrect order. The order should have been as follows: Orly N. Elpeleg, MD; Varda Barash, PhD; Haggit Hurvitz, MD; and David Branski, MD.

Bone Mineral Content in Black and White Children 1 to 6 Years of Age

Early Appearance of Race and Sex Differences

Jie-Ying Li, MD; Bonny L. Specker, PhD; Mona L. Ho, MS; Reginald C. Tsang, MBBS

• Bone mineral content was determined in 131 children, 1 to 6 years of age, in a prospectively designed cross-sectional study. Using multiple linear regression analysis to control for individual factors, bone mineral content was higher in black children compared with white children, was lower among female children compared with male children, increased with age, and increased with weight. (AJDC. 1989;143:1346-1349)

Measurement of bone mineral content (BMC) in the forearm by photon absorptiometry is a simple and precise method to study the amount of mineral in bone.^{1,2} It has been widely used in normal subjects and in patients with metabolic bone disorders. In childhood, BMC increases significantly with age.^{3,4} Differences by sex also have been studied; in one study, male infants had higher BMC than female infants.⁵ In another study, Specker and coworkers⁴ demonstrated that among white children, boys and girls have similar BMC from 1 to 4 years of age, but girls have significantly lower BMC at 5 to 6 years of age. However, there is currently a lack of normative data of BMC in healthy black children 1 to 6 years of age. Available data indicate that bone mass is increased in black, as compared with white, adolescents and adults^{6,7} and that skeletal development (as measured by appearance of ossification centers) of black children (aged 1 to 7 years old) is advanced in comparison with that of white children.⁸ Racial differences in BMC, however, have not been exam-

ined in early childhood. We hypothesized, in this prospective study of 131 children 1 to 6 years of age, that (1) black children would have higher BMC compared with white children; (2) BMC would be lower in female children compared with male children; and (3) BMC would increase with increasing age.

SUBJECTS AND METHODS

Subjects

Seventy-eight black and 53 white children 1 to 6 years of age were recruited for this prospectively designed cross-sectional study from the well-child clinic at the Children's Hospital Medical Center, Cincinnati, Ohio, from December 1987 to March 1988. This study population is distinct from a previously studied group of predominantly white children who were recruited from private pediatric practices and examined for BMC.⁴ Information on gestational age, sex, race, date of birth, history of breast-feeding, and current use of vitamin supplements was obtained from the parent. All children were term at birth and none of them had known major congenital abnormalities, bone disorders, or significant gastrointestinal disease and renal disease. All children were between the fifth and 95th percentile on the Boston growth curves.⁹ No blood samples were obtained for study.

Multiple linear regression techniques were used to determine differences between groups and correlation among variables. The partial correlation coefficients for each of the significant factors in the regression analysis are given. The partial correlation is the amount of variability explained by that factor after the other factors are included in the model. The protocol was approved by the Institutional Review Board of the Cincinnati Children's Hospital Medical Center and parental informed consent was obtained.

Photon Absorptiometry

The BMC and bone width (BW) were measured by a direct photon absorptiometer (Lunar Radiation Inc, Madison, Wis). A collimated, 2-mm-diameter photon beam from

low-activity monochromatic radionuclide source (iodine 125) passed beneath the on third distal radius (shaft) of the left forearm. The detection site was located by external measurement. A collimated scintillation detector placed over the arm was equipped with a mechanism to allow for simultaneous movement of the collimated detector and ¹²⁵I source, with a scan speed of 0.5 mm per second in children under 3 years of age and 1 mm per second in children over 3 years of age. The child's forearm was placed in a holding device and surrounded by a water bag to maintain constant thickness across the measuring path. At least three scans were obtained for each child and the mean value was obtained. The attenuation of detected counts is proportional to the mass (grams per centimeter) of mineral in the scan path; B is proportional to the length of the scan path. The accuracy of the photon absorptiometer when compared with ashed bones for BMC is high (error, 2% to 4%) with a high precision (error, 2%).¹ Our coefficient of variation for phantom standards is less than 1.5%.

RESULTS

Seventy-eight children (59.5%) were black, and 48.9% of the children were male. Thirty-three percent of children were receiving vitamin supplements containing vitamin D at the time of the study. The average age of those receiving vitamins was 38 months. Twenty-one (16%) of the children had been breast-fed, with an average weaning age of 28 weeks. There were no racial differences in the percent of children currently receiving vitamin supplements (30% of black children and 38% of white children, $P = .4$) or previous breast-fed (13% of black children and 25% of white children, $P = .09$). Mean BMC and BW were not different between children taking vitamin supplements or not, even after controlling for other variables significantly associated

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Bone Mineral Content (BMC), Bone Width (BW), BMC/BW, Height, and Weight by Race, Sex, and Age*

Race/Sex	Variable	Age, mo		
		12-35	36-59	60-83
B/M	No. of subjects	18	13	4
	BMC, g/cm	0.213 ± 0.031	0.306 ± 0.057	0.412 ± 0.099
	BW, cm	0.806 ± 0.072	0.895 ± 0.083	0.950 ± 0.103
	BMC/BW, g/cm ²	0.265 ± 0.035	0.341 ± 0.049	0.429 ± 0.053
	Height, cm	85.5 ± 7.1	100.7 ± 5.6	110.3 ± 4.5
	Weight, kg	12.8 ± 2.0	17.2 ± 2.0	18.4 ± 2.0
B/F	No. of subjects	19	14	10
	BMC, g/cm	0.186 ± 0.051	0.293 ± 0.057	0.356 ± 0.057
	BW, cm	0.775 ± 0.143†	0.878 ± 0.074	0.953 ± 0.064
	BMC/BW, g/cm ²	0.235 ± 0.050	0.333 ± 0.048	0.373 ± 0.052
	Height, cm	84.4 ± 7.7	102.9 ± 8.2	114.8 ± 4.0
	Weight, kg	12.0 ± 1.9	15.8 ± 2.5	20.3 ± 2.5
W/M	No. of subjects	13	8	3
	BMC, g/cm	0.208 ± 0.046	0.274 ± 0.057	0.334 ± 0.058
	BW, cm	0.786 ± 0.067	0.870 ± 0.064	0.879 ± 0.105
	BMC/BW, g/cm ²	0.263 ± 0.050	0.314 ± 0.053	0.382 ± 0.064
	Height, cm	84.4 ± 8.6	102.5 ± 4.8	112.4 ± 6.8
	Weight, kg	12.3 ± 2.0	17.6 ± 1.3	20.3 ± 2.6
W/F	No. of subjects	9	12	3
	BMC, g/cm	0.160 ± 0.042	0.244 ± 0.051	0.337 ± 0.043
	BW, cm	0.719 ± 0.143	0.853 ± 0.047	0.926 ± 0.190
	BMC/BW, g/cm ²	0.220 ± 0.038	0.287 ± 0.065	0.368 ± 0.031
	Height, cm	82.3 ± 5.0	99.9 ± 7.3	115.0 ± 4.0
	Weight, kg	11.4 ± 1.6	16.1 ± 2.0	20.7 ± 1.1

*Data were analyzed using a multiple general linear model that statistically controls for the influence of other factors on BMC. Race ($P < .001$), sex ($P = .02$), age ($P < .001$), and weight ($P < .001$) were found to be independent predictors of BMC. Data are presented in 2-year age groupings for reference.

†The number of subjects was 18 for this measurement.

with BMC. In the multiple-regression model presented below, children who were previously breast-fed had a higher BMC than children not previously breast-fed ($P = .03$). However, one black male child, 6.7 years of age and previously breast-fed, had a high BMC (0.559 g/cm). When he was omitted from the analysis, the only difference in the findings was that the relationship between history of breast-feeding and BMC was no longer statistically significant. The results presented below include this data point, but history of breast-feeding has not been included in the final statistical model due to the questionable relationship resulting from inclusion of data on one child.

The age, sex, and race distributions, as well as the mean BMC, BW, BMC-to-BW ratio, weight, and height, are given in the Table. Two-year age groupings were used in the Table due to the small numbers of children in each race and sex

group if categorized into 1-year age groups. Female children weighed less than male children ($P = .02$) after adjusting for age. There was no difference in weight between black and white children.

Age, sex, race, and weight were found to be independently associated with BMC (overall $R^2 = .771$). The BMC was higher in black children compared with white children (partial $R^2 = .114$, $P < .001$), was lower in female children (partial $R^2 = .044$, $P = .02$), and increased with age (partial $R^2 = .110$, $P < .001$) and weight (partial $R^2 = .193$, $P < .001$). We had previously found a smaller increase in BMC with age in female children compared with male children⁴; this relationship, tested by the interaction of age and sex, was not observed in the current study, and female children had a lower BMC at all ages compared with male children (Figure).

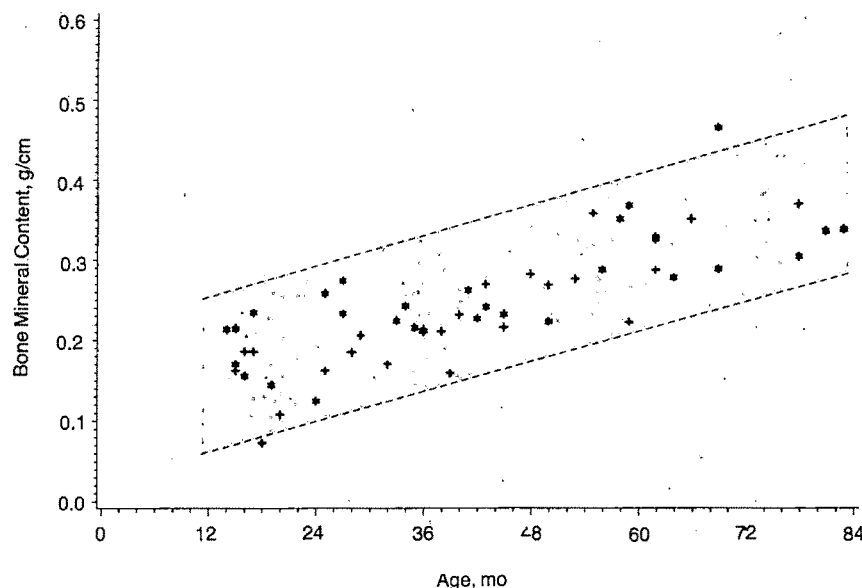
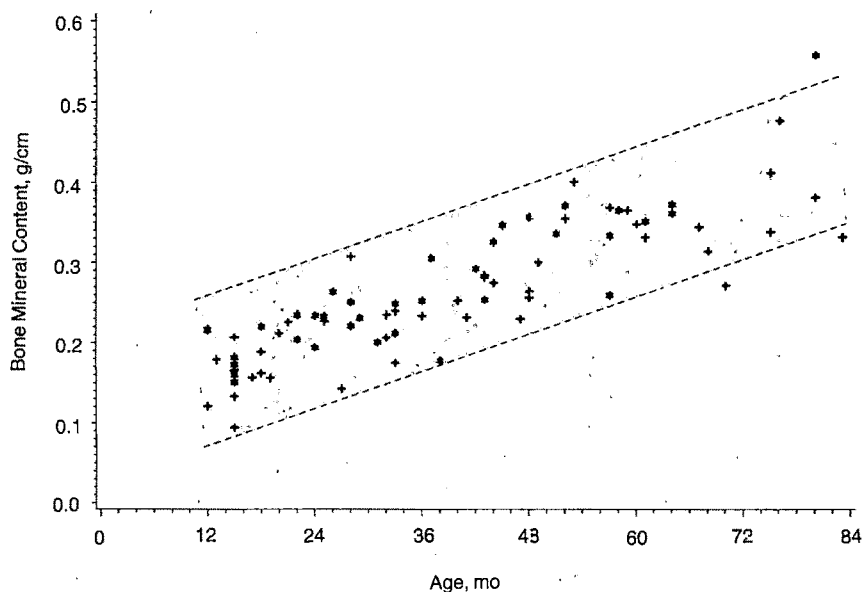
Bone width increased with increasing weight (partial $R^2 = .343$, $P < .001$) and was greater in black children compared with white children (partial $R^2 = .032$, $P = .04$). Bone width was greater in older compared with younger children (in univariate analysis); however, weight was a stronger predictor of width than age and age was not included in the final model. Results for the ratio of BMC to BW were similar to those obtained for BMC.

COMMENT

Photon absorptiometry has been shown to be a precise and accurate method for determining BMC in both adults and infants. It also has made a great contribution to the understanding of clinical factors influencing bone mineralization. In children, the method has been used to (1) determine the effects of various factors on BMC, such as sex,^{8,9} age,^{4,10,11} and nutrition,^{6,12} and (2) quantify effects of diseases on BMC, especially in bone disorders.^{13,14}

In this study, we demonstrated that BMC was not associated with history of breast-feeding or current use of vitamin supplements. Breast-feeding has been associated with BMC that is lower than that of formula-fed infants during the first 6 months,¹⁵ but there is little information on the influence of early breast-feeding on BMC in later childhood. The small percent of children who had been breast-fed had similar BMC to those children who had not been breast-fed.

To our knowledge, normative data of BMC in black children are not available. In the present study, black children 1 to 6 years of age had higher mean BMC than white children. In earlier studies, black infants and children have been found to have advanced skeletal development, as measured by the presence of ossification centers, compared with white infants and children.⁸ It has been suggested that the higher bone mass in blacks is due to a larger body mass, which results in increased strain on the skeleton, which would then stimulate bone formation.¹⁶ However, black adult women have 10% to 20% greater total body calcium and phosphorus compared with white women even after adjusting for body weight.⁷ Our current findings support a race difference in BMC independent of body weight. The reason for



Bone mineral content by year of age for each race and sex. Bone mineral content: was higher in black (top) compared with white (bottom) children ($P < .001$), increased with increasing age ($P < .001$), and was lower in female (plus sign) compared with male (asterisk) children ($P = .03$). Increased body weight also was found to be associated with higher bone mineral content ($P < .001$) independent of the other factors.

this difference is not clear since factors other than genetic may influence BMC (ie, diet).

White female children of varying ages have been found to have lower BMC compared with male children.^{3,6} In the current study, there was significantly lower BMC in female children compared with male children 1 to 6 years of age. In our previous study of BMC in white children from private pediatric practices,

we observed a lower BMC among female children compared with male children only after 4 years of age.⁴ The reason for sex differences in BMC is unclear but does not appear to be related to differences in body weight since in our analysis sex differences were still apparent after statistically controlling for the influence of weight.

In the present study, BMC increased with increasing age. Increases in BMC

with increasing age have been demonstrated in children 1 to 14 years of age,^{3,4} and our study is consistent with these reports. Weight also was found to have an independent influence on BMC and may be due to the increased strain on the skeleton resulting in increased bone formation.¹⁷

Findings concerning the ratio of BMC to BW were similar to those of BMC. It has been suggested that the ratio of BMC to BW reduces variation and would be of more value in determining the difference between an individual and the normal population, whereas BMC is a better measurement to follow in an individual for bone mineral changes.¹⁸ However, several studies demonstrated that a BMC-to-BW ratio is not a more sensitive indicator than BMC.^{13,18,19}

In view of the current findings, race- and sex-specific BMC norms would be helpful when BMC is used as a tool for diagnosing disordered bone mineralization. Anecdotally, rickets appears to be identified in the United States more in black than white infants and children^{20,22}; it might be important to recognize that norms for BMC are different between races when assessing BMC in such infants. For example, black infants with rickets may have BMC that appears normal by white infant studies, but may be low by black infant norms.

In summary, differences in BMC by race, sex, age, and weight were observed; BMC was higher in black compared with white children, was lower in female than in male children, and increased with age and weight.

This research was supported by Thrasher Research Training Program (Salt Lake City, Utah) in Nutrition Fund 2799-0, Perinatal Research Institute (Cincinnati, Ohio), and National Institutes of Health (Bethesda, Md) grant HD 20748.

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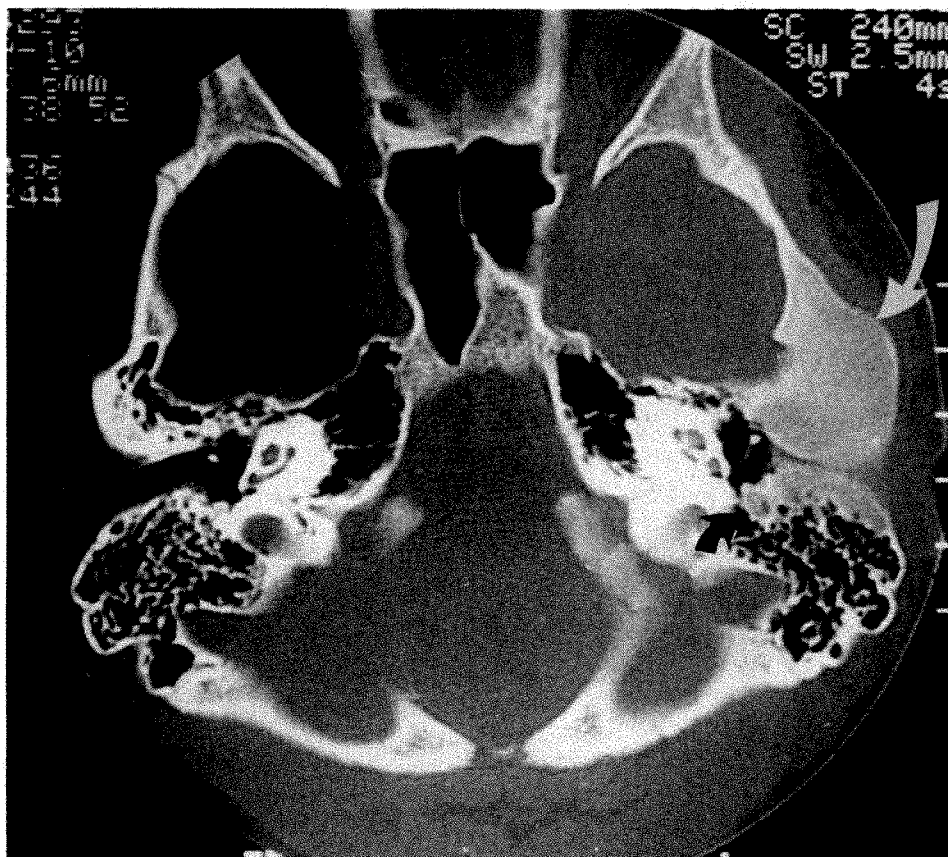
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Radiological Case of the Month

Yoav P. Talmi, MD; Jacob Bar Ziv, MD; Rosa Shimberg, MD; Yehuda Finkelstein, MD;
Yuval Zohar, MD (*Contributors*); Beverly P. Wood, MD (*Section Editor*)



A 15-year-old girl was admitted for evaluation of fullness of her left ear. Her physician had made a diag-

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Contributed from the Departments of Otolaryngology (Drs Talmi, Shimberg, Finkelstein, and Zohar) and Radiology (Dr Ziv), Hasharon Hospital, Golda Medical Center, Petah Tikvah, Israel.

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nosis of left external otitis. The physical examination results were normal except for an extremely narrowed left external auditory canal. The narrow lumen was engulfed by bony overgrowth, and no local edema or signs of inflammation were seen. Audiologic evaluation demonstrated a moderate conductive hearing loss. A computed tomographic scan of the region was performed (Figure).

Denouement and Discussion

Monostotic Fibrous Dysplasia of the Temporal Bone

Computed tomographic scan demonstrating narrowing of the left external auditory canal caused by an expansile bone lesion of the temporal bone (curved arrow). The regional bone was characterized by a "ground-glass" appearance. A small cholesteatoma is located between the tympanic membrane and the bony lesion (black arrow).

The patient underwent surgical exploration of the ear. The nearly obliterated lumen was widened, and the canal was cleaned of cholesteatoma debris found trapped between the eardrum and the narrowed bony isthmus. Histologic sections confirmed the diagnosis of fibrous dysplasia.

Fibrous dysplasia is a congenital, locally circumscribed nondifferentiation of bone-forming mesenchyme. The lesion is characterized histologically by a proliferation of fibrous tissue and scattered trabeculae of immature bone. The disease has three clinical forms: (1) monostotic, which is isolated to one bone; (2) polyostotic, which affects two or more bones; and (3) Albright's syndrome, which is a polyostotic form associated with abnormal skin pigmentation, precocious puberty, and other nonskeletal manifestations. The disease usually becomes manifest in late childhood when lesion growth accelerates rapidly, only to become quiescent, in most in-

stances, after puberty. This uncommon disease rarely involves the temporal bone.^{1,2}

The roentgenographic features of fibrous dysplasia are usually characteristic and in a series of 46 consecutive cases of fibrous dysplasia of the craniofacial skeleton were found in each case to correlate accurately with the pathologic analysis.³ The roentgenographic examination reflects the morphologic nature of the disease and the results vary with the amount of fibrosis and calcification present. Areas of fibrosis and cyst formation produce radiolucency, whereas areas of new bone formation demonstrate increased density. In many instances, local expansion in the temporal bone is seen associated with either sclerosis or a uniform "ground-glass" appearance.^{1,2} Occasionally, areas of radiolucency and cortical thinning are seen and constriction or even obliteration of the external auditory canal can be regularly demonstrated. Computed

tomographic scanning provides good detail of the extent of the disease. An accurate assessment of the degree of middle-ear involvement and of the presence of associated cholesteatoma can be made.⁴

In our case the computed tomographic scan demonstrated the extent of the disease and the existence of a cholesteatoma. The combined findings of roentgenograms and computed tomography established the diagnosis of fibrous dysplasia, which was later confirmed by pathologic study.

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Picture of the Month

Paruathi U. Iyer, MBBS, MD, Neena Vaswani, MBBS, MD (*Contributors*); Murray Feingold, MD (*Section Editor*)

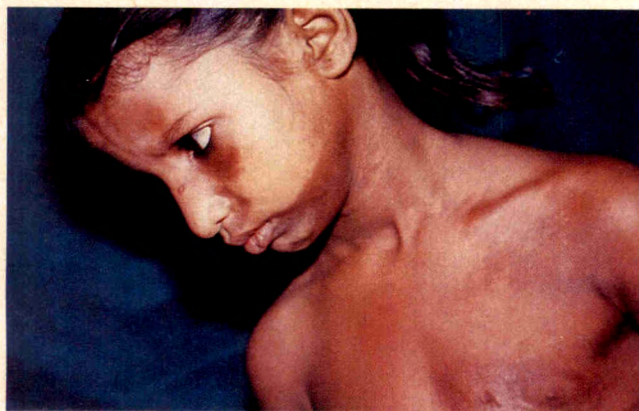


Figure 1.

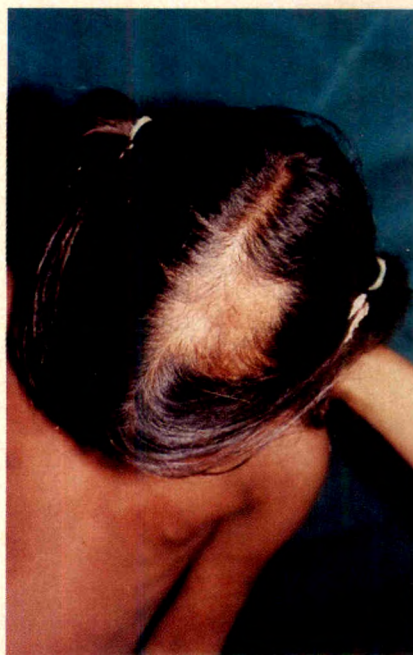


Figure 2.



Figure 3.

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Denouement and Discussion

Morphea

Fig 1.—Hyperpigmented lesions and facial atrophy.

Fig 2.—Cicatricial alopecia.

Fig 3.—Multiple hyperpigmented lesions on the trunk.

Manifestations

Morphea, also called linear scleroderma, is a form of scleroderma that has a patchy focal distribution. Initially, the lesions are slightly erythematous and edematous or may have an atrophic, shiny appearance. Subsequently, they appear as ivory-colored indurated plaques with violaceous borders. The lesions usually first appear on the trunk and spread to the limbs. Scarring and fibrosis occur, which can lead to contractures and apparent shortening of limbs.

The disease may progress for years or arrest after several months of activity. In dark-skinned individuals, the scars may become hyperpigmented, and in others, the atrophic areas may become hypopigmented. Lesions on the scalp may produce cicatricial alopecia, and facial hemiatrophy occurs

due to sclerosis of the facial muscles. Erosion of the underlying bone may also occur.

Microscopic examination reveals sclerosis associated with varying degrees of inflammation involving the dermis and occasionally extending to the subcutaneous tissue and panniculus. Eosinophilia, elevated sedimentation rate, and low complement may be present. Antinuclear antibodies and rheumatoid factor are present in 5% to 15% of the cases.

Causative Factors

Trauma and drugs such as valproic acid have been reported as possible causative factors. Immunologic or vascular injury and altered collagen metabolism are suggested mechanisms. There does not appear to be any genetic predisposition.

Treatment

No effective treatment is presently available. A variety of medications have been used, such as D-penicillamine, corticosteroids, salicylates, chelating agents, chloroquine phosphate, and radiation, without any definite benefit. The disease usually follows a slow, indolent course, and the cicatricial process gradually becomes passive. Prognosis for life is usually good, unless there is systemic involvement, which is unusual.

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Early Diagnosis of Spastic Diplegia, Spastic Hemiplegia, and Quadriplegia

Susan R. Harris, PhD, PT

• A retrospective study examined early neurodevelopmental behaviors of children with spastic diplegia, spastic hemiplegia, and quadriplegia (spastic, athetoid, or mixed) who had been followed up longitudinally in a high-risk infant follow-up clinic. Compared with peers with normal outcomes, children with all three types of cerebral palsy had significantly lower scores on the Bayley Mental Scale at 4 months of age; children with hemiplegia and quadriplegia also scored significantly lower on the Bayley Motor Scale. On the Movement Assessment of Infants at 4 months of age, the children with hemiplegia and quadriplegia showed significantly higher risk scores than the nonhandicapped group. The Movement Assessment of Infants was more than three times as sensitive as the Bayley Motor Scale in detecting motor abnormalities in 4-month-old infants with diplegia and more than twice as sensitive in detecting early abnormalities of hemiplegia. At 1 year of age, however, the Bayley Motor Scale was extremely sensitive in picking up motor deficits in children with all three types of cerebral palsy.

(AJDC. 1989;143:1356-1360)

Although controversy continues about whether the prevalence of cerebral palsy (CP) is increasing among very-low-birth-weight infants, Kitchen and colleagues¹ maintain that the prevalence is "unacceptably high," with a rate of 12.5% of spastic CP among 2-year-old survivors at their hospital. Diagnosis of CP during infancy is extremely difficult, particularly in mild to moderate cases,^{2,3} which accounted for approxi-

mately two thirds of the children in the recent study by Kitchen et al.¹ Definitive diagnosis during infancy of three common types of CP, spastic diplegia, spastic hemiplegia, and quadriplegia (spastic, athetoid, or mixed), has not, to my knowledge, been reported in the literature. The purpose of this study was to identify retrospectively a variety of developmental markers that could serve to differentiate these three types of CP during the first year of life. Subjects were children who were part of a prospective, longitudinal high-risk infant follow-up project at the University of Washington, Seattle, from 1976 to 1985.

Hypotheses in this study were as follows: (1) Children with spastic diplegia, spastic hemiplegia, and quadriplegia differed significantly from nonhandicapped (NH) children on the Bayley Mental and Motor Scales.⁴ (2) Children with spastic diplegia, spastic hemiplegia, and quadriplegia differed significantly from NH children on categorical risk scores and total risk scores of the Movement Assessment of Infants (MAI).⁵ (3) The Bayley Motor Scale was sensitive to early diagnosis of spastic diplegia, spastic hemiplegia, and quadriplegia at 4 months' and 12 months' corrected ages. (4) The MAI was sensitive to early diagnosis of spastic diplegia, spastic hemiplegia, and quadriplegia at 4 months' corrected age.

In addition, the average ages for definitive diagnoses of each of these types of CP were examined. Recent articles have suggested that reliable diagnosis of spastic diplegia does not occur until 18 to 24 months of age in the United States,⁶ and that for children with congenital hemiplegia, the average age of referral for developmental evaluation at a center in England was 22 months.⁸

METHODS

Subjects and Methods

The original sample consisted of 399 infants who had been evaluated initially between 1976 and 1981 in the University of Washington's Neonatal Intensive Care Unit Followup Clinic. Entry criteria included birth weight of 1500 g or less, a history of idiopathic respiratory distress syndrome, or any other clinical condition posing a high risk for abnormal development, such as central nervous system infection or insult.

Infants were scheduled for evaluation at the following ages (corrected for prematurity): 4, 12, 24, 36, 54, 72, and 96 months. There were 399 infants who were evaluated initially between 3 months 15 days' corrected age and 4 months 14 days' corrected age; 229 (57.4%) of these children were followed up at least through the 36-month corrected-age visit. Due to reported difficulties in reliably diagnosing CP at 1 year of age⁹ and sometimes even later,^{5,8} it was decided that subject selection would be limited to those children for whom both medical and psychological follow-up data were available at 3 years of age or older.

Review of the follow-up records showed that approximately 80% of the infants unavailable for follow-up appeared normal at their last visit with the other 20% having been labeled as either questionable or abnormal.⁴ These findings are similar to those of Aylward and colleagues,¹⁰ which suggested that handicapped infants are no more likely to continue in follow-up than infants who are developing normally.

Assessment Tools

At their initial follow-up visit at 4 months' corrected age, infants were assessed by clinic physical therapists using the Mental and Motor Scales of the Bayley Scales of Infant Development, a standardized, norm-referenced tool, and the MAI, a neuromotor assessment tool that has been shown to be both reliable^{11,12} and valid¹³ in the evaluation of high-risk infants. The MAI consists of 65 items divided across four categories: muscle tone, primitive reflexes, automatic reactions, and

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volitional movement. Based on a 4-month profile developed from a small sample of infants,⁷ 48 of the 65 items can be scored as either "risk" or "no risk." Categorical risk scores are then derived for each of the four categories and are ultimately summed to attain a total risk score.

A variety of outcome measures were administered at the follow-up visits between 36 and 96 months of age. Developmental pediatricians assessed the children using the Denver Developmental Screening Test¹⁴ and a nonstandardized neurological examination that evaluated muscle tone and motor and speech development. Developmental psychologists used various standardized psychometric tests according to the child's corrected age: the Stanford-Binet Intelligence Scale,¹⁵ the Wechsler Preschool and Primary Scale of Intelligence,¹⁶ the Wechsler Intelligence Scale for Children-Revised,¹⁷ and the Peabody Picture Vocabulary Test.¹⁸ At the 54-month visit, occupational therapists assessed the children's motor development and coordination using an assessment protocol that included the gross motor portion of the Peabody Developmental Scales,¹⁹ the Frostig Eye-Motor Coordination subtest,²⁰ and portions of the Southern California Sensory Integration Test.²¹ All examiners were aware of the child's previous developmental test scores; no attempt was made to blind them to the child's developmental history.

Outcome Groups

Chart reviews were conducted for the 229 children who were followed up to at least the 36-month-old visit. Based on scores on standardized tests as well as medical diagnoses provided by the pediatricians when appropriate, the following three groups were defined: CP ($n=36$), developmental delay ($n=75$), and NH ($n=118$). Children in the CP group were further divided into three diagnostic categories: spastic diplegia ($n=14$), spastic hemiplegia ($n=11$), and quadriplegia ($n=11$), which included spastic, athetoid, and mixed (spastic/athetoid) cases. In addition to the type of CP, the severity was determined by the developmental pediatricians based on the following criteria: (1) mild was defined as no use of mechanical aids for ambulation, the child functions without obvious impairment; (2) moderate was defined as no need for mechanical aids for ambulation, but the child functions with obvious impairment; (3) severe was defined as the child ambulates only with mechanical aids; and (4) profound was defined as no ambulation.

Children in the group labeled "developmental delay" had a mixture of deficits ranging from mild motor delays or expressive language disorders to moderate mental retardation. Children in the NH group were those who performed within normal limits on

all developmental tests and who were deemed "normally developing" by the pediatricians at their latest follow-up visit.

Data Analysis

The first two hypotheses were examined by performing Student's t tests between each of the CP categories (spastic diplegia, spastic hemiplegia, and quadriplegia) and the NH group. The final two hypotheses were addressed by calculating the sensitivity of each tool in correctly identifying motor abnormalities at 4 months' (Bayley Motor Scale and MAI) and at 12 months' (Bayley Motor Scale) corrected ages. Also calculated were the mean ages and ranges for diagnoses of spastic diplegia, spastic hemiplegia, and quadriplegia.

RESULTS

Although the children with spastic diplegia were significantly smaller at birth than their NH counterparts, they were not significantly younger (Table 1). Whereas the children with spastic hemiplegia tended also to be smaller and younger than the children in the NH group, neither of these differences was significant. In contrast, the children with quadriplegia were remarkably similar in mean birth weight and gestational age to the NH group. With the exception of one infant in the hemiplegic group and one infant in the quadriplegic group, all of the other infants were born at less than 37 weeks' gestation (Table 1).

On the Bayley Scales of Infant Development, the 4-month-old children with spastic diplegia scored significantly lower than their NH age-matched counterparts on the Bayley Mental Scale (Mental Developmental Index [MDI]) but not on the Bayley Motor Scale (Psychomotor Developmental Index [PDI]). The mean scores for the MDI and PDI for the children with spastic diplegia were well within normal limits

(mean = 100), although the SD for the PDI was greater than the normative SD of 16. The 4-month-old children with spastic hemiplegia scored significantly lower than the NH group on both the MDI and the PDI; however, both mean scores for these developmental indexes were well within normal limits. In contrast, the children with quadriplegia scored significantly below the mean for both the mental and motor scales and were significantly different from their NH peers.

These differences can be accounted for, in part, by the differences in severity levels among the three groups. Whereas 64% of the children with diplegia were judged to be mild or mild to moderate in involvement and 82% of the group with hemiplegia were similarly rated, only 27% of the children with quadriplegia were so rated. These disparities suggest that it is the relative severity of involvement as well as the type of CP that appears to affect performance on the Bayley Scales (Table 2).

On the MAI at 4 months' corrected age, there were no significant differences between the children with spastic diplegia and the children in the NH group on any of the four categorical risk scores or on the total risk score. However, the children with spastic hemiplegia differed significantly from the NH children ($P<.05$) on three of the five scores: the categorical risk scores for automatic reactions and volitional movement and the total risk score (Table 3).

The sensitivity of the Bayley Motor Scale at 4 and 12 months' corrected ages was assessed by dividing the number of correctly identified abnormal cases at each age into the total number of abnormal cases and then multiplying this fraction by 100.²² For the Bayley Motor Scale, an abnormal score would be a

Table 1.—Birth Weight and Gestational Age Characteristics

Group	Birth Weight, g				Gestational Age, wk			
	n	Mean	SD	t	n	Mean	SD	t
Nonhandicapped	108	1787.94	668.50		112	32.66	2.94	
Spastic diplegia	12	1330.83	284.84	-4.38*	14	30.93	2.95	-2.07
Spastic hemiplegia	11	1440.46	793.83	-1.40	11	30.18	4.05	-1.98
Quadriplegia	9	1834.00	938.18	.15	9	32.33	2.00	-.45

* $P<.001$.

PDI of less than 84 (Table 4). The specificity of the Bayley Motor Scale at 4 months of age or its ability to correctly identify infants as normal who subsequently were judged to be normal at 36 to 96 months of age has been reported previously as 94.9%.²³

The sensitivity rate of the Bayley Motor Scale improved markedly at 12 months of age, particularly for the diplegic and hemiplegic groups. This dramatic improvement in sensitivity may have been due to the evolving clinical nature of CP rather than to deficiencies in the test at earlier ages.

The MAI was administered only at 4 months' corrected age. According to the MAI manual, total risk scores of 0 to 7 are considered "low risk," with scores of 8 to 12 being "at risk," and scores equal to or greater than 13 identified as "high risk" for motor problems.⁷ To examine the sensitivity of the MAI total risk score at 4 months of age, the number of correctly identified "at-risk" and "high-risk" infants (scores ≥ 8) were divided into the total number of infants who were subsequently diagnosed with diplegia, hemiplegia, or quadriplegia (Table 5). The specificity of the MAI at 4 months of age was 62.7%, which suggests that more than one third of the children who were subsequently judged to be NH had either suspect or abnormal total risk scores at 4 months of age.²³

The mean age at diagnosis for infants with spastic diplegia was 12.58 months (range, 4 to 30 months); approximately two thirds of these infants' conditions were rated mild or mild to moderate in severity. For the children with spastic hemiplegia, 82% of whom were labeled mild or mild to moderate, the average age of diagnosis was 21 months, with a range from 4 to 54 months of age. In contrast, the mean age for diagnosis of the infants with quadriplegia was 4.91 months, with a range from 1 to 10.5 months of age. This is not surprising since about 73% of the infants in this group were given severity ratings ranging from moderate to profound.

COMMENT

The first hypothesis was partially supported in that children in all three CP categories differed significantly from the children in the NH group with regard to scores on the Bayley Mental

Scale. Children with hemiplegia and quadriplegia differed significantly from the NH group on the Bayley Motor Scale as well. Although the children with spastic diplegia had lower Bayley Motor scores than the NH children, this difference failed to reach significance at the .05 level. The lack of a significant difference may be due to the relatively small sample size.

Although both the mean MDI and PDI scores for the children with hemiplegia were significantly below those for the NH children, they were both within the normal range. In fact, only 3 of the 11 children scored below the normal ranges on the mental and motor scales. Five children in this group showed cognitive delays (IQ < 85) at their latest follow-up visits as did 5 children in the spastic diplegic group.

Both the mean MDI and PDI scores were well below the normal ranges for the children with quadriplegia at both 4 and 12 months' corrected ages and significantly different from those of their NH age-matched counterparts. At 12 months of age, all 9 children tested scored below 84 on both the MDI and the PDI. However, 3 of the 11 children had IQ scores within normal limits at their latest follow-up visits. Since the Bayley Mental Scale involves many fine motor items, it is not surprising that the children's MDIs were compromised by their upper-extremity motor handicap. Clinicians should use caution when using the Bayley Mental Scale for children with upper-extremity motor handicaps since it may not provide an accurate reflection of cognitive skills.

The second hypothesis was supported in part for children with hemiplegia and

in its entirety for children with quadriplegia. The children with hemiplegia differed from the NH group on the MAI total risk score and two of the four categorical risk scores. Children in the quadriplegic group had significantly higher risk scores in all four categories, as well as in the total risk score. Although the children with spastic diplegia did not differ significantly from the NH children on the MAI total risk score or any of the categorical risk scores, results of an item analysis reported previously showed that these two groups did differ on seven of the MAI items: posture prone, posture supine, muscle tone summary, trunk rotation, equilibrium responses in prone, summary of automatic reactions, and vocalization.⁴ This suggests that a shorter version of this test should be developed specifically for the early detection of spastic diplegia.

For the children with spastic hemiplegia, significantly higher categorical risk scores were noted in the categories of automatic reactions and volitional movement when compared with children with normal outcomes. These findings imply that the assessment of automatic or postural reactions and volitional movement items, specifically the ability to center the head in the supine position and the ability to bear weight through the shoulders when placed in the prone position,⁴ are important neurodevelopmental attributes that should be examined in infants at risk for hemiplegia.

As Table 5 shows, the infants with quadriplegia scored significantly higher than their normally developing peers on all five risk scores. Many of these chil-

Table 2.—Bayley Scale Scores at 4 Months Corrected Age

Group	Mental Developmental Index				Psychomotor Developmental Index			
	n	Mean	SD	t	n	Mean	SD	t
Nonhandicapped	116	107.46	15.40	...	116	106.16	16.34	...
Spastic diplegia	13	95.31	17.02	-2.46*	14	99.79	29.25	-0.80
Spastic hemiplegia	11	88.91	14.78	-3.96†	11	91.46	15.02	-3.08*
Quadriplegia	9	65.56	17.13	-7.12‡	10	69.80	18.00	-6.17‡

* $P < .05$.

† $P < .01$.

‡ $P < .001$.

Table 3.—MAI* Scores at 4 Months Corrected Age

MAI Risk Category	Non-handicapped (n = 108)		Spastic Diplegia (n = 11)		t	Spastic Hemiplegia (n = 11)		t	Quadriplegia (n = 8)		t
	Mean	SD	Mean	SD		Mean	SD		Mean	SD	
Tone	1.86	2.12	3.73	3.29	1.84	3.64	2.66	2.15	7.00	2.62	5.42†
Primitive reflexes	1.98	1.82	3.18	2.32	1.67	2.64	2.06	1.01	8.00	3.29	5.11†
Automatic reactions	1.80	1.46	2.55	2.38	1.02	3.36	2.29	2.22‡	6.38	1.69	7.48§
Volitional movement	1.30	1.54	1.64	1.43	1.84	3.55	2.73	2.69‡	7.88	3.00	6.15§
Total Risk Score	6.94	5.19	11.09	7.30	1.84	13.18	8.32	2.44‡	29.25	9.51	6.56§

*MAI indicates Movement Assessment of Infants.

† $P < .01$.

‡ $P < .05$.

§ $P < .001$.

Table 4.—Sensitivity of the Bayley Motor Scale
(Psychomotor Developmental Index < 84)*

Type of Cerebral Palsy	% (No.) of Subjects	
	4 mo Corrected Age	12 mo Corrected Age
Spastic diplegia	15.4 (2/13)	100 (12/12)
Spastic hemiplegia	27.3 (3/11)	75 (6/8)
Quadriplegia	60.0 (6/10)	100 (9/9)

*Specificity at 4 months was 94.9% (111/117).²³

Table 5.—Sensitivity of the
Movement Assessment of Infants
(Total Risk Score ≥ 8)*

Type of Cerebral Palsy	% (No.) of Subjects 4 mo Corrected Age
Spastic diplegia	57.1 (8/14)
Spastic hemiplegia	63.6 (7/11)
Quadriplegia	90.9 (10/11)

*Specificity at 4 months was 62.7% (74/118).²³

dren had motor problems so obvious at 4 months of age that testing was used primarily to confirm the diagnosis; a detailed description of this group's performance on the MAI individual items has been reported previously.⁴

The final two hypotheses addressed the sensitivity of the Bayley Motor Scale and the MAI in the early detection of the three types of CP. The MAI was clearly superior in identifying more than three times as many children with diplegia at 4 months of age (57.1% vs 15.1%) and more than twice as many children with hemiplegia (63.6% vs 27.3%). The MAI sensitivity for early quadriplegia was about 1.5 times as great as for the Bayley Motor Scale. At 1 year corrected age, however, the Bayley Motor Scale was very sensitive to all three types of CP. Previous research has shown that although the MAI was more sensitive than the Bayley Motor Scale at 4 months of age, it tended to have a lower rate of specificity in that a greater percentage of children with normal outcomes were labeled "at risk."²³

In spite of the very high sensitivity of

the Bayley Motor Scale at 1 year corrected age, it is interesting to note that a definitive diagnosis of CP was not made until much later for the children with spastic hemiplegia (mean age, 21 months). This discrepancy represents caution on the part of our pediatric staff in avoiding unnecessary alarm for the parents.²⁴ In spite of the fact that a diagnosis of CP was not made until after 1 year of age for almost one third of the children with diplegia and hemiplegia, 95% of our children with CP were referred for early intervention services by age 1 year.

CONCLUSIONS

The goal of this study was to retrospectively identify developmental markers that would allow for the detection of three common types of CP during infancy. Assessment tools administered at 4 months' corrected age included the Bayley Mental and Motor Scales and the MAI. While children with quadriplegia differed significantly from low-birth-weight infants with normal developmental outcomes on all parameters of

the Bayley and MAI, neither of these tools had complete success in differentiating children with either spastic diplegia or spastic hemiplegia from their NH peers.

Infants with hemiplegia, however, showed significantly higher MAI risk scores in the categories of automatic reactions and volitional movement and in the total risk score. Both the hemiplegic and diplegic groups showed significantly lower MDIs, with the hemiplegic group also showing a significantly lower PDI when compared with the NH group. The mean developmental indexes were all within normal ranges, however. The total risk score of the MAI was considerably more sensitive in the identification of motor disorder at 4 months of age than was the PDI (Bayley Motor Scale), but the PDI was highly sensitive for all three groups at 12 months' corrected age.

In spite of the fact that the prevalence of CP seems to be increasing among low-birth-weight infants,^{1,25,26} little progress has been made in reliable early diagnosis of this disability. Recently published

retrospective studies have suggested that there are specific early neuromotor behaviors that are predictive of CP,^{4,27} but a definitive assessment tool has yet to be developed that has a high rate of both sensitivity and specificity.

While this study suggests that the MAI is more sensitive than the Bayley

Motor Scale in detecting early signs of CP, the generalizability of these results is limited by the small sample size and the retrospective nature of this study. Further prospective research is needed with larger samples to substantiate these findings. In addition, it would be interesting to study the relative sensi-

tivity and specificity of these standardized neurodevelopmental tests compared with more traditional neurological examinations.

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In Other AMA Journals

JAMA

The Epidemiology of Injuries in Atlanta Day-care Centers

J. J. Sacks; J. D. Smith; K. M. Kaplan; D. A. Lambert; R. W. Sattin; R. K. Sikes
(*JAMA*. 1989;262:1641)

Adolescents and Their Music

E. F. Brown, W. R. Hendee (*JAMA*. 1989;262:1659)

Infectious Medical Wastes

Council on Scientific Affairs (*JAMA*. 1989;262:1669)

Correction of Atrioventricular Septal Defect

Results Influenced by Down Syndrome?

Thijs W. Vet, Jaap Ottenkamp, MD

• The role of Down syndrome (DS) in the outcome of the surgical correction of atrioventricular septal defect (AVSD) was investigated by the analysis of clinical events among 85 patients. Complete AVSD (cAVSD) was present in 49 patients, of whom 36 (73%) had DS. Thirty patients (83%) survived surgical treatment. Of the 13 patients without DS, 7 (54%) survived. There were four deaths and one late death. Thirty-six patients had partial AVSD (pAVSD), 5 (14%) of whom had DS; all 5 patients are still alive. Thirty (97%) of the 31 patients with pAVSD without DS survived the operation. There were two late deaths. Preoperative selection did not account for the favorable results in children with DS. All early postoperative deaths in cAVSD occurred in children younger than 2 years; low body weight for age seemed to be an important factor in adverse outcome. A large number of patients without DS had other serious congenital malformations. In view of the relatively favorable results in patients with DS, it does not seem warranted to maintain a conservative diagnostic and therapeutic approach of AVSD solely because of concomitant DS.

(AJDC.1989;143:1361-1365)

Atrioventricular septal defect (AVSD), a serious congenital heart malformation, is known to be relatively common in children with Down syndrome (DS). It is estimated that in 40% of children with DS, a congenital heart defect is part of the syndrome and that in 40% of patients with DS and a congenital heart defect, the defect is an AVSD.^{1,2} Furthermore, in DS the complete form of AVSD is more common than the partial form (also known as

"primum type atrial septal defect"), while the reverse is true for the general population.

Recently, several reports have noted that the cardiac malformation in children with AVSD and DS is less complicated than in children with AVSD only. Obstruction of the outflow tract of the left ventricle especially seems to be less frequent and less severe in children with DS.^{3,4} However, Sondheimer et al⁵ reported that the diagnostic and surgical care offered to children with DS and AVSD is often incomplete. Along with other factors, defeatism as to the therapeutic (surgical) possibilities in children with DS can be blamed for this inequality. From a surgical viewpoint, a too conservative diagnostic approach to these children would be unjustified if the relatively optimistic reports^{3,4} on the anatomy of the AVSD in DS were true.

We have asserted our clinical impression that children with DS actually did better after surgical correction of their AVSD than did children without DS. To validate this impression, a comparison of the results of the surgical correction of AVSD in the Leiden clinic (the Netherlands) between children with DS and those without DS was conducted. As DS is not a criterion in the diagnostic process and preoperative selection in our medical center, we are convinced that we can rule out an uneven selection of patients as a source of bias.

PATIENTS AND METHODS

We reviewed the medical records of 85 children consecutively treated for an AVSD by surgical correction in the years 1976 through 1987 in Leiden University Hospital, the Netherlands. The group was divided into the following four subgroups: 36 patients with DS and a complete AVSD (DS-cAVSD), 13 patients without DS with a complete AVSD (NDS-cAVSD), 5 patients with DS

and a partial AVSD (DS-pAVSD), and 31 patients without DS with a partial AVSD (NDS-pAVSD).

For cAVSD and pAVSD separately, we compared the surgical results between patients with and without DS. The diagnosis of DS was based on the typical findings on physical examination and was confirmed by chromosome analysis.

As cAVSD causes much more severe symptoms than pAVSD, and does so at a much earlier age, and as the surgical correction of cAVSD is more complex, it is necessary to make a distinction between the complete and the partial forms. The cAVSD clinically consists of a defect of the atrial and ventricular septum and an unseparated atrioventricular valve that is shared by the left and right sides of the heart. In the pAVSD, the septal defect is limited clinically to the atrial septum, and separate left and right atrioventricular valves are present. The valves, however, are abnormally formed, and, as in the complete form, are malfunctioning.

Attention was given to the postoperative period and to the most recent information available on each patient.

RESULTS

All 85 medical records of our patients were carefully checked for concomitant congenital defects apart from DS and AVSD. Table 1 shows all the anomalies diagnosed before surgery, during surgery, or at postmortem examination. Certain cardiac and noncardiac malformations had already been treated surgically before correction of the AVSD.

Age and weight at operation for each of the patients in the four subgroups are given in Table 2. In Table 3, the same variables are shown for patients with cAVSD treated before their second birthday.

The surgical procedure was the same throughout the entire study period. In cases of cAVSD, separate patches were

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Table 1.—Cardiac and Noncardiac Malformations, Apart From DS and AVSD, Found in the Total Patient Group*

Patient No.	Sex	Malformations	
		Cardiac	Noncardiac
DS-cAVSD			
1	M	CoAo, PDA, and retroesophageal subclavian artery	...
3	M	TOF	...
5	M	TOF	...
6	F	ASD II and PDA	...
8	M	ASD II	...
9	F	PDA	...
10†	M	PDA	...
11	F	Multiple small ASDs	...
13	F	TOF and small accessory VSDs	Duodenal Atresia
14	M	PDA	...
15	F	PDA	...
16	F	PDA	...
17†	F	ASD II and PDA	...
22	F	Valvular PS	...
24	M	Parachute mitral valve and ASD II	
25†	F	Mesocardia and hypoplastic LV	Left isomerism
29†	F	TOF, ASD II, and right descending aorta	...
30	M	TOF	...
31	F	PDA	...
33	F	Infundibular PS	...
35†	F	ASD II and PDA	...
36	M	ASD II and PDA	...
NDS-cAVSD			
51†	M	PDA	Malrotation and microcephaly
52	M	ASD II	Noonan's syndrome
53	M	ASD II	...
54	M	TOF and persistent left VCS	...
55†	M	...	Atypical auricles
56	M	Persistent left VCS	Mohr's syndrome
57†	M	Hypoplastic LV, LVOTO, PDA, and azygos connection	Polysplenia syndrome
58	F	Dextrocardia, AV discordance, atrial situs ambiguous, DORV, infundibular PS, and persistent right VCS	Total situs inversus
59†	F	Congenital AV block, valvular PS, PDA, absent right VCS, and hemiazygos connection	Left isomerism
60	M	Valvular PS	...
62†	M	Hypoplastic LV, CoAo, PDA, partial anomalous pulmonary venous connection, and hemiazygos connection	Holt-Oram syndrome
63†	F	CoAo and retroesophageal subclavian artery	Pierre Robin syndrome, esophageal atresia, arachnodactyly, and absent olfactory nerve

used for repair of the atrial and ventricular septum, while the adjacent atrioventricular valve leaves were "sandwiched" between these patches (double-patch sandwich technique). In pAVSD, the interatrial defect was closed by one patch. In cAVSD and pAVSD, modifi-

cations to the atrioventricular valves were tailored to each individual situation, aimed at obtaining optimal valve function.

Mortality in the hospital (number of deaths occurring within 30 days after surgery) for cAVSD was high. Six (17%)

of 36 patients with DS-cAVSD and 6 (46%) of 13 patients in the NDS-cAVSD group died (difference not significant, $P = .08$, χ^2 test)—a total of 12 deaths (24%) in 49 patients (Table 4).

All the patients who died were younger than 2 years. When only the 34 patients with cAVSD who were operated on before their second birthday are considered, mortality in the hospital was 6 (23%) of 26 for patients with DS-cAVSD and 6 (75%) of 8 for patients with NDS-cAVSD (difference is significant, $P = .02$, χ^2 test).

One of the 36 patients with pAVSD who did not have DS died. In the hospital, mortality was 0% for the DS-pAVSD group, 3% for the patients with NDS-pAVSD (difference not significant, $P = .68$, χ^2 test), and 3% for the complete pAVSD group (Table 4).

A second surgical procedure was necessary in 19 patients—6 in the DS-cAVSD group, 2 in the NDS-cAVSD group, and 11 in the NDS-pAVSD group. In most cases, this operation consisted of a second attempt at repair of the "mitral" valve or implantation of a valve prosthesis in this position. One patient with NDS-cAVSD died during the second surgical procedure.

Of the 19 patients who underwent repeated surgery, 5 had a third procedure (1 with DS-cAVSD, 1 with NDS-cAVSD, and 3 with NDS-pAVSD); all 5 patients underwent implantation or replacement of a mitral valve prosthesis. At this third operation, one patient with NDS-pAVSD died.

There were three late deaths in the DS-cAVSD group (all caused by infectious diseases). In the NDS-cAVSD group, the infant who died at reoperation for mitral valve replacement was the only instance of a late death. No late deaths occurred in the DS-pAVSD group, while two late deaths were noted in the NDS-pAVSD group (one after a second reoperation for mitral valve replacement, and one while awaiting such a procedure).

Survival at the time of this study, therefore, was 27 (75%) of 36 patients with DS-cAVSD, 6 (46%) of 13 patients with NDS-cAVSD (difference not significant, $P = .12$, χ^2 test), 5 (100%) of 5 patients with DS-pAVSD, and 28 (90%) of 31 patients with NDS-pAVSD (difference not significant, $P = .47$, χ^2 test).

The follow-up period for these survivors varied from 1 to 130 months, with a mean of 41 months (Table 5).

COMMENT

The uneven distribution of the 85 patients in this study among the four subgroups clearly mirrors the difference in the natural occurrence of cAVSD and pAVSD in children with and without DS. This does not facilitate a comparison in which DS is the variable factor.

Three results, to us, were striking. First, there was a low mortality in the hospital for pAVSD (1 [3%] of 36 patients). Because this figure is so low and because the number of patients with DS-pAVSD both absolutely and relatively was small, a comparison for pAVSD between children with and without DS was impossible.

Second, we found an abundance of congenital malformations besides DS and AVSD in this patient group. It would seem that AVSD, as a rule, is part of a complex of congenital anomalies, both cardiac and noncardiac. An AVSD is generally known as the typical congenital heart defect of DS. As the results of our study show, DS is the single most frequent syndrome in children with AVSD. However, a large proportion of children without DS in this study had other serious congenital anomalies; in a number of cases these anomalies represented recognizable syndromes. To our knowledge, this phenomenon has not been reported previously. We are aware that a retrospective study of surgical results will not generate sufficient data on the natural occurrence of concomitant malformations in AVSD. The frequency of concomitant malformations in this study is high, but because of the uniqueness of each of these anomalies in this study group, their contribution to mortality in the hospital could not be established.

Third, mortality of patients with DS-cAVSD (17%) and patients with NDS-cAVSD (46%) in the hospital greatly differ, as do their long-term survival rates (75% and 46%, respectively).

We also found that all deaths occurred in children younger than 2 years. All children with cAVSD are usually operated on before that age to prevent irreversible pulmonary hypertension. This policy has also been adopted in our cen-

Table 1.—Cardiac and Noncardiac Malformations, Apart From DS and AVSD, Found in the Total Patient Group* (cont)			
Patient No.	Sex	Malformations	
		Cardiac	Noncardiac
NDS-pAVSD			
151	F	Persistent left VCS	Oligophrenia and atypical habitus
152	F	Double-orifice mitral valve	...
153	M	Infundibular and valvular PS and small accessory VSD	Hypospadias and cryptorchism
154	M	Dextrocardia and persistent right VCS	...
155	F	Subvalvular aortic stenosis	...
159	F	Double-orifice mitral valve	Ellis-van Creveld syndrome
161	M	Persistent left VCS	Esophageal atresia
162	M	Persistent left VCS to left atrium and absent coronary sinus	Psychomotor retardation and polydactyly
166	M	CoAo and double-orifice mitral valve	Clubfeet
168	F	Valvular PS and double-orifice mitral valve	...
169	F	Accessory VSD	...
170	F	Subvalvular aortic stenosis	Situs inversus
171	F	PDA and aberrant course VCI	...
172	F	Persistent left VCS	...
174	F	CoAo, small accessory VSD, and PDA	Hypothyroidism
178	M	Double-orifice mitral valve	...
180	F	ASD II	...
181	M	CoAo, hypoplastic aortic arch, and ASD II	...

*DS indicates Down syndrome; AVSD, atrioventricular septal defect; DS-cAVSD, patients with Down syndrome and a complete atrioventricular septal defect; NDS-cAVSD, patients without Down syndrome with a complete atrioventricular septal defect; NDS-pAVSD, patients without Down syndrome with a partial atrioventricular septal defect; ASD II, atrial septal defect, secundum type; AV, atrioventricular; CoAo, coarctation of the aorta; DORV, double-outlet right ventricle; LV, left ventricle; LVOTO, left ventricular outflow tract obstruction; PDA, patent ductus arteriosus; PS, pulmonary stenosis; TOF, tetralogy of Fallot; VCI, inferior vena cava; VCS, superior vena cava; and VSD, ventricular septal defect. No patients are listed with Down syndrome and a partial atrioventricular septal defect.

†Hospital death.

Characteristics	DS-cAVSD	NDS-cAVSD	DS-pAVSD	NDS-pAVSD
No. of patients	36	13	5	31
Age, mo				
Range	4-186	2-128	33-236	3/4-179
Mean	26	37	128	74
Median	11	11	126	60
Body weight, kg				
Range	4.3-60.0	3.4-26.0	13.0-51.0	2.7-56.0
Mean	10.2	10.4	33.4	19.5

*DS-cAVSD indicates patients with Down syndrome and a complete atrioventricular septal defect; NDS-cAVSD, patients without Down syndrome with a complete atrioventricular septal defect; DS-pAVSD, patients with Down syndrome and a partial atrioventricular septal defect; and NDS-pAVSD, patients without Down syndrome with a partial atrioventricular septal defect.

ter; 26 of the 36 patients with DS-cAVSD and 8 of the 13 patients with NDS-cAVSD underwent surgery before the age of 2 years. The percentage of children with DS in this group of 34

(76%) is comparable with that in the total group of 49 patients with cAVSD (73%).

The difference in mortality in the hospital between patients with DS-cAVSD

Table 3.—Age and Weight at the Time of Operation for Patients With cAVSD*

Characteristics	DS-cAVSD†	NDS-cAVSD†
No. of patients	26 (6/20)	8 (6/2)
Age, mo		
Range	4-19 (5-19/4-15)	2-13 (2-13/2-8)
Mean	9 (11/9)	6 (6/5)
Median	9 (12/8)	4 (4/5)
Body weight, kg		
Range	4.3-8.5 (4.3-8.2/4.8-8.5)	3.4-6.7 (3.6-6.5/3.4-6.7)
Mean	6.3 (6.2/6.4)	4.8 (4.7/5.1)

*Patients with a complete atrioventricular septal defect (c-AVSD) who were operated on before the age of 2 years. DS indicates patients with Down syndrome, and NDS, patients without Down syndrome.

†Total No. of patients (No. dead within 30 days after surgery [hospital death]/No. of survivors after 30 days following surgery).

Table 4.—Details on Hospital Deaths.*

Patient No./Age, mo/Body Weight, kg	Cause of Death
DS-cAVSD	
2/19/6.8	Low output
10/6/4.3	Pneumonia
17/5/4.7	Low output
25/11/5.4	Low output
29/15/8.2	Septicemia
35/12/7.7	Pneumonia
NDS-cAVSD	
51/8/4.0	Low output
55/2/5.1	Cerebral damage after cardiopulmonary arrest
57/13/6.5	Septicemia
59/5/5.0	Low output
62/3/3.9	Was considered inoperable during surgery and died in operating room
63/3/3.6	Pneumonia
NDS-pAVSD	
177/4/4.3	Septicemia and cerebral hemorrhage

*DS-cAVSD indicates patients with Down syndrome with a complete atrioventricular septal defect; NDS-cAVSD, patients without Down syndrome with a complete atrioventricular septal defect; and NDS-pAVSD, patients without Down syndrome with a partial atrioventricular septal defect.

Table 5.—Summary of the Surgical Results for All Four Subgroups*

Characteristics	DS-cAVSD	NDS-cAVSD	DS-pAVSD	NDS-pAVSD
No. of patients operated on	36	13	5	31
No. (%) of hospital deaths	6 (17)	6 (46)	0 (0)	1 (3)
Second operations	6	2	0	11
Third operations	1	1	—	3
Late deaths during second or third operation	0	1	—	1
Other	3	0	0	1
No. (%) of long-term survivors	27 (75)	6 (46)	5 (100)	28 (90)
Follow-up period, mo				
Range	3-103	1-102	9-58	1-130
Mean	42	37	33	42

*DS-cAVSD indicates patients with Down syndrome and a complete atrioventricular septal defect; NDS-cAVSD, patients without Down syndrome and a complete atrioventricular septal defect; DS-pAVSD, patients with Down syndrome with a partial atrioventricular septal defect; and NDS-pAVSD, patients without Down syndrome with a partial atrioventricular septal defect.

and patients with NDS-cAVSD operated on before their second birthday (23% and 75%, respectively) is significant ($P = .02$). In this age group, there was a tendency for lower body weights in children without DS. Mean body weight at the time of operation for children younger than 2 years with DS was 6.3 kg, while children without DS at that time had a mean body weight of 4.8 kg (Table 3).

We do not consider the low body weight for age in itself to be the cause of high mortality in the hospital, and thus the explanation for the unfavorable results in patients without DS. More probably, failure to thrive and the high mortality rate share common causative factors.

One of these factors could well be the more severe and often complicated malformation of the heart with AVSD in children without DS.^{3,4} Of the 13 patients with NDS-cAVSD, 3 had a hypoplastic left ventricle, a coarctation of the aorta, or both (patients 57, 62, and 63). All 3 patients were operated on before the age of 2 years and all 3 died. On the contrary, of the 36 patients with DS-cAVSD, only 1 had a hypoplastic left ventricle (patient 25), and 1 other patient had a coarctation of the aorta (patient 1). Both were operated on before their second birthday; the patient with the hypoplastic left ventricle died. Clearly, obstruction of the left ventricle and of its outflow caused an increased surgical risk, notably influencing mortality in the hospital. It is likely that, through failure of the left side of the heart, also due to a larger left-to-right shunt, a more significant failure to thrive may occur.

A hypoplastic left ventricle is a contraindication for correction of cAVSD. Unfortunately, especially the milder forms of right ventricular dominance are difficult to diagnose before surgery.

The factors that might explain the large difference in mortality in the hospital between children with and without DS certainly deserve further research in a prospective study design. We are convinced that a referral or selection bias does not play a role in the advantageous results in children with DS. It is not common practice in any hospital in our region to deny surgery to patients with DS. Furthermore, this study

group included many patients without DS with other serious congenital malformations; if there would have been a referral bias, they also would have suffered from it. According to some, a mild hypothyroidism protects the myocardium of patients with DS during heart surgery. We do not expect that this influence is important. In our experience, the postoperative management of children with DS certainly is not easier. They often require longer periods of postoperative intensive care.

We direct future research toward an explanation for the failure of patients with cAVSD without DS to thrive. Often the clinical condition of these children deteriorates under maximum conservative therapy, and one is forced to attempt surgical repair of the cAVSD, which is a high-risk operation, at a very young age.

We cannot set general rules as to the indication for surgical correction of AVSD in multihandicapped children based on our data, nor do we want to.

From a purely surgical viewpoint, chances for children with AVSD and DS are good, even better than average. In determining individual therapeutic policy, yet other considerations might have to be considered. However, it seems unwarranted to state that DS in general seriously complicates surgical correction of an AVSD.

Koos Zwinderman, PhD, provided us with statistical advice.

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In Other AMA Journals

ARCHIVES OF SURGERY

Rhabdomyosarcoma: Contemporary Status and Future Directions: The Lucy Wortham James Clinical Research Award

Sarah S. Donaldson, MD (*Arch Surg.* 1989;125:1015-1020)

Resident Hours: Only Work?

Robert E. Condon, MD (*Arch Surg.* 1989;125:1121-1122)

Treating the Trauma Patient

F. William Blaisdell, MD (*Arch Surg.* 1989;125:1122)

Vaginal Opening Measurement in Prepubertal Girls

Christopher W. Goff, MD; Kenneth R. Burke, MD; Christina Rickenback, RN, CPNP; Donald P. Buebendorf, MD

• Normative, age-indexed data regarding the size of the vaginal opening in prepubertal girls have not been previously reported, to our knowledge. Measurement of the apparent transverse diameter of the vaginal opening was done in 273 prepubertal girls as part of their routine health assessment. Vaginal opening diameter tended to enlarge with age and to be larger in the supine knee-chest position than in the supine frog-leg position. An opening greater than 4 mm was distinctly rare. (AJDC. 1989;143:1366-1368)

A vaginal opening with a transverse diameter of greater than 4 mm in a prepubertal girl has been said to be abnormal¹⁻³ and strongly correlated with a history of sexual abuse.^{1,2,4} This claim has profound implications, both legal and medical. Unfortunately, although gynecology texts state that the maximum normal transverse diameter of the vaginal opening, also referred to as the (horizontal) diameter of the hymenal orifice⁵ or vaginal introital diameter,⁴ is 4 to 7 mm in prepubertal girls,^{5,6} not only are supporting studies not cited, but nearly 55% of physicians are either unaware of, or disagree with, the veracity of the textbooks' claims.⁷ A review of the literature verifies that normative data about female genitalia, particularly regarding the transverse diameter of the vaginal opening, are sadly lacking.

Cantwell,² in the follow-up to her original study of 247 prepubertal girls evaluated in a unit designed for children who had been sexually or physically abused or neglected, which reported that 74% of those patients with a transverse vaginal diameter of greater than 4 mm had a history of sexual abuse, noted that only 6 (4%) of 158 girls in that unit who denied having been sexually abused had a transverse diameter of the vaginal opening greater than 4 mm.

In a study of 242 girls between the ages of 1 and 12 years, 144 of whom had a history of sexual abuse or gonococcal infection, White et al⁴ found that 5% of the 75 girls without such a history, but considered "at risk," had a vaginal opening with a transverse diameter greater than 4 mm. None of the 23 girls in the control group had a measurement greater than 4 mm.

As part of a larger study, Emans et al⁸ described a group of 34 girls between the ages of 3 and 6 years, with neither genital complaints nor a history of sexual abuse, who had a mean (\pm SD) vaginal opening of 2.9 ± 1.3 mm (range, 1 to 6 mm). This closely corresponded to the overall control group of 127 girls aged 1 to 14 years in whom the vaginal opening averaged 2.8 ± 1.5 mm. These investigators also reported that the vaginal opening tended to enlarge with age, although complete, age-indexed data were not presented.

Cantwell¹ has pointed out that "accurate measurement (of the vaginal opening) presents problems since the vagina is an elastic organ and the anteroposterior diameter is difficult to measure." Herman-Giddens and Frothingham⁹ have noted that since the moist folds of the hymen may stick together, simple inspection is not adequate to view the vaginal opening. Rather, several seconds of lateral and slight posterior traction are usually required for the hymenal folds to fall apart, allowing visualization of the vaginal opening. Both tension and time of traction might therefore be expected to affect the apparent opening size. Although several authors⁸⁻¹⁰ have stated that there is a significant difference in transverse diameter of the vaginal opening depending on the position (eg, supine frog-leg [SFL], supine knee-chest [SKC], prone knee-chest) that the child is in during measurement, to our knowledge this has not been systematically studied. In view of these issues, it should be understood that the term *vaginal opening* in this report refers specifically to the apparent transverse diameter of the vaginal

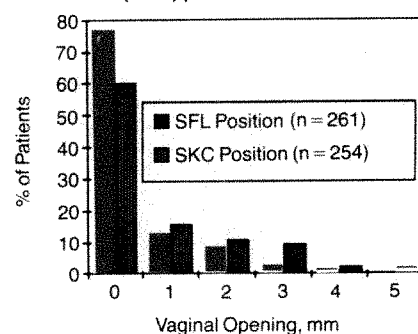
opening.

All of the published studies focus primarily on populations of girls who have either a history of being sexually abused or factors that make that diagnosis more likely. Furthermore, they have reported measurements without apparent regard to position during examination, standardization of technique, or age. The control groups described are few in number and may not be representative of the population seen in an average private practice. Therefore, Herman-Giddens and Frothingham⁹ concluded that "normative data on [vaginal opening in] nonabused prepubertal girls needs to be gathered . . . Whether the opening in the hymen slowly increases in diameter . . . is not absolutely known because there are no . . . studies . . ." Our study was designed to provide clinical data on the apparent transverse diameter of the vaginal opening in the SFL and SKC positions in prepubertal girls seen in a private pediatric practice setting using standardized techniques applicable to that setting.

METHODS

As part of routine health maintenance examinations, girls in our pediatric practice have their genitalia inspected. During this examination, in addition to careful inspection of the vulva, labia, clitoris, perineal area, and hymen, the transverse diameter of the

Distribution of vaginal opening measurements in supine frog-leg (SFL) and supine knee-chest (SKC) positions.



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vaginal opening is noted.

To make the procedure nonthreatening, the child is told that "her bottom needs to be checked," and that checking involves both gentle touching and using a flashlight (otoscope) to see better. The patient is instructed to lie down on her back (if not already there), then directed to "bend your knees and put your heels by your bottom; now let your knees fall apart so you look like a frog." The thumbs or index fingers are placed at the midpoint of the labia majora and gentle traction is applied laterally (moving the labia 1 to 1.5 cm on each side) and slightly (0.5 cm) dorsally.

Approximately 4 seconds are given to allow the vaginal opening to reach its maximum size. This time period was arbitrarily chosen as a standard because of clinical experience that most dilatation takes place within the first 1 to 2 seconds, and that cooperating for longer periods of traction is difficult for some young girls. If the hymenal folds fall apart allowing an opening to be seen, the traction is maintained by using the thumb and index finger of the left hand, while a millimeter rule is placed next to the vaginal opening. The transverse diameter of this opening at the level of the hymen is then noted to the nearest millimeter. This measurement is the same as the horizontal hymenal diameter if hymenal tissue is present.

As we often use an otoscope light to allow better visualization of the area, for convenience we taped the measuring device, a 2-cm section of the plastic rule used to read tuberculin tests, flat on the top of the otoscope head. After the measurement has been taken, the child is asked to put her legs together, flex her hips, and hug her knees to her chest, thus placing her in the SKC position, and the procedure is repeated. The entire standardized procedure is a modification of that illustrated and outlined in detail by Herman-Giddens and Frothingham.³

Measurements were prospectively recorded in all girls younger than 8 years of age having routine physical examinations in our office between June 1, 1988, and October 31, 1988. All examinations were done by one of us. While the study design did not allow multiple examiners to measure each child undergoing a routine physical examination, interobserver reliability was checked by comparing the means and variances of the age-indexed measurements found by the different examiners.

RESULTS

Our population base is primarily white (90% to 95%), with small numbers of black (3% to 5%), Hispanic (<3%), and Asian (<3%) youngsters. The majority of families are middle- and upper-

Age, y	No. of Patients	Mean Measurement, mm	SD	Maximum Measurement, mm	Minimum Measurement, mm
SFL Position					
<1	72	0.17	0.47	2	0
1	44	0.23	0.57	2	0
2	31	0.16	0.45	2	0
3	25	0.24	0.72	3	0
4	29	0.45	0.69	2	0
5	23	0.78	1.28	4	0
6	15	0.60	0.83	2	0
7	22	1.23	1.19	4	0
Total	261	0.41	0.85	4	0
SKC Position					
<1	70	0.26	0.63	3	0
1	41	0.29	0.60	2	0
2	30	0.37	0.72	3	0
3	25	0.60	1.08	3	0
4	29	1.24	1.24	4	0
5	22	1.82	1.37	4	0
6	15	1.33	1.29	3	0
7	22	2.50	1.47	5	0
Total	254	0.85	1.25	5	0

Age, y	No. of Patients	Mean Difference, mm	SD	Maximum Difference, mm	Minimum Difference, mm
<1	70	0.09	0.28	1	0
1	41	0.10	0.37	1	-1
2	30	0.20	0.48	2	0
3	25	0.36	0.86	3	0
4	29	0.79	1.01	3	0
5	22	1.00	1.07	3	0
6	15	0.73	0.88	3	0
7	22	1.27	1.03	4	0
Total	254	0.43	0.80	4	-1

middle class, although at least 7% are covered by state welfare. Two hundred seventy-three girls were examined as part of a routine health assessment. All girls were prepubertal (ie, had Tanner stage I breast and pubic hair development). All hymenal types were included.

Twelve girls were excluded from further analysis because they presented with genital complaints¹⁰ or had tight labial adhesions preventing adequate examination.² Seven other girls (2.7%) had measurements recorded for only the SFL position. In one of these cases, the child refused examination in the

SKC position. All of these children were less than 20 months old. If girls had more than one routine health assessment during the study period, only the first examination for which complete data were obtained has been included.

Results of the findings are shown in the Figure. The distribution of diameters of the vaginal opening was strikingly skewed toward 0 mm. Median and mode values of the vaginal opening in the SFL position were 0 mm until the eighth year. In the SKC position, these values were 0 mm until the fifth year. No patient had a vaginal opening of greater than 4 mm in the SFL position

(indeed, all but two were 3 mm or less), and only three 7-year-old girls did in the SKC position (all three had a 5-mm vaginal opening). The mean vaginal opening in both the SFL and SKC positions increased with age from 0.17 mm (SFL) and 0.26 mm (SKC) in the first year to 1.23 mm (SFL) and 2.50 mm (SKC) in the eighth year (Table 1).

Comparing the vaginal opening as measured in the SFL and SKC positions showed the measurement in the SKC position to be equal or larger than that in the SFL position, except in one case. The difference in measurements in the two positions (SFL value minus SKC value) varied from -1 mm to 4 mm, with mean differences ranging from 0.09 mm to 1.27 mm. Both the mean and SD increased with age (Table 2).

Forty-six girls were examined on more than one occasion. All were under 20 months of age. The measurements obtained varied by a mean of 0.17 mm (SD, 0.53 mm) for measurements obtained in the SFL position and 0.29 mm (SD, 0.58 mm) in the SKC position. We were unable to demonstrate any significant interobserver differences by comparing age-indexed measurements using the analysis of variance (ANOVA) and multiple Student's *t* tests ($P \geq .20$).

COMMENT

We have presented age-indexed data for apparent transverse diameter of the vaginal opening in prepubertal girls in a small-town pediatric practice in Connecticut. Although generalizing our results to all racial or socioeconomic groups should be done with great care, our findings document the assertion that a vaginal opening greater than 4 mm (over 5 mm in girls 7 years of age or older in the SKC position) is distinct-

ly uncommon, and therefore support those researchers who consider it to be abnormal. The data differ from norms previously published.^{4,6,8,11,12} Since these authors neither presented the data used to establish their conclusions nor described a standard technique used in examination of the children (in fact, in several studies, multiple positions were used for measurement^{1,2,3,18}), any attempt to explain the difference would be purely speculative.

In spite of some authors' claims that a vaginal opening of greater than 4 mm should cause one to suspect sexual abuse, no conclusions from our study can be drawn about the causes of an opening greater than 4 mm. Furthermore, it must be stressed that a vaginal opening of less than or equal to 4 mm neither ensures nor suggests that a child has not been sexually abused. Although many authors have made this point,^{1,3,4,7,8-10,14,15} it needs to be stressed.

When reporting and interpreting vaginal opening measurements, particularly in legal proceedings involving possible sexual abuse, care must be taken to either follow our protocol exactly or to specify the position, timing, and order in which the child was examined. We used SKC and SFL positions that we, as others,^{5,12} find less frightening to the child, and which should not be confused with the *prone* knee-chest position recommended by some authors.^{1,16} Our own anecdotal experience concurs with that of Emans et al⁸ who stated that "because the hymenal ring dilates and gapes in the [prone] knee-chest position, measurements should be done in the supine position."

Contrarily, this experience implies that the prone knee-chest position may be advantageous when more detailed inspection of the vagina is necessary in a

child with vaginal pathologic findings. While all but one of our patients had a vaginal opening in the SKC position that was greater or equal to that in the SFL position, this may have been due to the order in which the examination was performed. This possibility needs to be examined, as well as the possibility that a longer period of traction might have allowed for further relaxation and dilatation of the vaginal opening.

The possibility that the vaginal opening associated with one type of intact hymen might be less than that with another (for example, redundant or "flower-petal" type compared with crescentic) was not studied. Furthermore, it should be noted that a vaginal opening of 0 mm does not mean that a girl had an imperforate hymen. Rather, as we did not attempt to separate the hymenal folds with a cotton swab or other instrument, our data suggest that with this standard inspection/examination technique, in many children the hymenal folds do not fall apart, and in those that do, a vaginal opening of greater than 4 mm is rare.

While our data suggest that the vaginal opening does not vary dramatically between examinations, our sample is small and further longitudinal study is indicated. In spite of the suggestion by some authors that a difference of 1 mm in vaginal opening is too small to be useful clinically,⁸ all of the investigators in our study found it surprisingly easy to make the distinction (even in the 0- to 3-mm range before using the measuring device), and found that patients cooperated for the examination. Therefore, we concur with Cantwell¹ who recommended that evaluation of the vaginal opening be included as an important element in the routine health assessment of prepubertal girls.

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Ultrasomic Imaging in the Differential Diagnosis of Diffuse Thyroid Disorders in Children

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• In 22 patients with suspected diffuse goiter, the diagnostic accuracy of ultrasonography was compared with that of aspiration biopsy cytology and thyroid antibody testing. Ultrasonography was abnormal in 100% (10/10) of the patients with autoimmune thyroid disease, only 90% (9/10) of whom were identified with antibody testing. All patients with diffuse colloid goiter had normal echo patterns on ultrasound imaging, whereas 29% (2/7) of them had positive results on antibody testing. Whether these are 'false positives' or represent focal thyroiditis remains unclear. Thus, ultrasound imaging stands out as a valuable diagnostic tool for the differential diagnosis of diffuse thyroid disorders in children.

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In adults, ultrasound imaging of the thyroid is accepted as the most sensitive noninvasive method for visualizing the internal anatomy of the thyroid gland.¹ With ultrasound, the normal thyroid is visualized as a smooth, rather echo-rich pattern of stronger echogenicity than the surrounding muscle tissue. The technique has been used successfully in distinguishing between cystic and solid nodules, between solitary and multiple nodules, and in measuring the size of the thyroid gland.¹⁻⁴ There have been several reports that the echogenicity of the thyroid decreases in patients with acute, subacute, and autoimmune thyroiditis. Pöyhönen and Lenko⁵ found ultrasound imaging to be valuable in the differential diagnosis of diffuse goiter in children, whereas Bachrach et al⁶ did not.

The aim of the present prospective study was to compare the accuracy of high-resolution ultrasound imaging with that of other available methods in the differential diagnosis of diffuse thyroid disorders in children.

PATIENTS AND METHODS

The series comprised 22 children (17 girls and 5 boys) ranging in age from 8 to 16 years, 19 of whom were attending the pediatric clinic because of suspected diffuse goiter. Of the remaining 3 cases, 1 came to light during a prospective study of the prevalence of thyroglobulin autoantibodies (Tgab) among children in the city of Malmö in southern Sweden. Ultrasound imaging was done before treatment, except in 2 patients in whom it was done about 1 year after the start of thyroxine (T₄) treatment.

Thyroid hormone analyses were done in accordance with routine procedures at the clinical laboratory. Total T₄ and total triiodothyronine (T₃) were measured with double-antibody radioimmunoassays.⁷ Thyrotropin was measured with an immunoradiometric assay (TSH RIA 200, Pharmacia, Uppsala, Sweden). Thyroglobulin autoantibodies were detected with a solid-phase immunosorbent radioassay.⁸ Microsomal antibodies were detected by immunofluorescence (Serodia AMC, Fujirebio, Tokyo, Japan). A radionuclide scan with technetium Tc 99m pertechnetate and aspiration biopsy cytology were performed in all cases.

The ultrasound imaging was performed by one of us (P.H.P.) who did not know the results of the other analyses. Ultrasonic examination was performed with a real-time ultrasound sector scanner (DRF 400, Diasonics, Milpitas, Calif) using a 10-MHz transducer. All children were examined while they were in the supine position with the neck extended. The thyroid was always investigated both in the transverse and longitudinal projections. The thyroid volume was expressed in milliliters by measuring the long axis and the transverse and anteroposterior diameters of both thyroid lobes. The size of the isthmus was not included in the calculation as it was found to contribute very little to the total thyroid volume. In cases where the long axis exceeded 30 mm (50%), the lobe had to be measured in two sections, as the transducer aperture was only 30 mm. The procedure used for measuring the long axis was as follows: The caudal limit of the thyroid lobe was located and positioned at the lower margin of the transducer aperture. A central structure was then selected on the long axis of the thyroid and its distance from the caudal limit measured. The transducer was then moved cranially along the long axis to reposition the chosen structure near the lower margin of the aperture, and its distance from the cranial limit of the thyroid

lobe was measured, the sum of the two measurements being taken as the dimension of the long axis. Although not entirely satisfactory, this procedure had to be adopted as no other high-resolution transducer with a wider-image angle was available.

The echo pattern of a normal thyroid gland is characterized by high-amplitude echoes uniformly scattered throughout the gland. The surface area is smooth. Reference values for thyroid gland volume had been established for children from 5 to 17 years of age and presented in a previous report.⁹

RESULTS

Aspiration biopsy cytology was performed in all children. Juvenile autoimmune thyroid disease (AITD) was confirmed in 10 patients, diffuse colloid goiter in 7 patients, and subacute thyroiditis (de Quervain's) in 1 patient. Although aspiration biopsy cytology findings were inconclusive in 4 patients, 1 patient showed changes both of AITD and the de Quervain type of thyroiditis. The diagnoses and results of antibody testings are given in the Table.

On the basis of the clinical and laboratory findings, all but 1 of the 22 children were euthyroid. Thyrotropin values were slightly high in 6 children, 4 of whom had AITD and 2 of whom had inconclusive biopsy findings. In all but 1 of the 10 patients with AITD, a goiter was suspected on palpation. In 8 of the patients, an enlarged gland was found on ultrasound imaging, and in 14 patients, the gland was considered to be enlarged at thyroid scintigraphy.

Ultrasound Findings

All patients with AITD on aspiration biopsy cytology had abnormal echo patterns with hypoechogenicity on the ultrasound image. The echogenicity was not homogeneous, with small areas of normal echoes surrounded by areas with low or very low echogenicity giving a patchy appearance. Essentially as outlined by Yoshida et al,¹⁰ though with minor modifications, the degree of abnormality was graded from 0 to 4 as follows: grade 0, diffuse—high amplitude echo throughout the lobe of the thyroid (normal) (Fig 1); grade 1, sim-

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The Results of the Thyroid Hormone Analyses, Antibody Testings, Scintigraphy, Ultrasound Imaging, and Aspiration Biopsy Cytology in 22 Children*

Patient No./Sex/ Age, y	T ₃ , nmol/L	T ₄ , nmol/L	Thyrotropin, mU/L†	Tgab Titer	Mab Titer	⁹⁹ Tc Scan	Ultrasound Image	Aspiration Biopsy Cytology
1/F/11	2.2	146	1.2	1:50	Neg	N	Subacute thyroiditis	Subacute thyroiditis
2/F/14	2.7	150	0.6	Neg	Neg	N	N	C
3/F/15	1.9	85	1.9	1:5000	Neg	N	AITD	AITD
4/F/15	1.7	84	0.6	Neg	Neg	N	N	C
5/F/14	2.6	100	2.0	1:5000	Neg	N	N	C
6/M/15	3.0	88	2.8	1:500 000	Neg	N	AITD	AITD
7/F/14	2.2	60	8.5	1:500	Neg	N	AITD	AITD
8/M/15	1.8	97	7.0	Neg	Neg	N	AITD	AITD
9/M/15	1.9	79	2.2	1:500	Neg	N	AITD	AITD
10/F/12	2.7	125	5.0	1:500	>1/6400	N	N	Inconclusive
11/F/12	2.5	78	5.0	1:500 000	>1/6400	D	AITD	AITD
12/F/12	2.7	79	4.0	1:50 000	Neg	D	AITD	AITD
13/F/9	1.8	95	4.0	1:500	1:160	D	AITD	AITD
14/F/14	1.8	97	1.8	1:5000	Neg	D	N	Inconclusive
15/F/12	2.3	77	2.0	1:5000	Neg	N	N	C
16/F/10	2.3	82	4.6	1:50 000	1/1600	D	AITD	AITD
17/F/15	2.0	85	6.0	1:5000	>1/6400	D	Subacute thyroiditis	Inconclusive
18/F/15	2.0	105	1.1	Neg	Neg	D	N	C
19/M/14	2.5	90	2.1	1:50 000	1:160	D	AITD	AITD
20/F/15	2.4	90	0.9	Neg	Neg	D	N	C
21/M/8	7.5	217	<0.1	1:5000	1:1600	N	AITD	Inconclusive
22/F/15	2.0	121	0.8	Neg	Neg	N	N	C

*T₃ indicates triiodothyronine (reference interval, 0.9 to 3.2 nmol/L); T₄, thyroxine (reference interval, 50 to 150 nmol/L); Tgab, thyroglobulin antibody; Mab, microsomal antibody; ⁹⁹Tc, technetium Tc 99m; Neg, negative; N, Normal; C, colloid goiter; AITD, autoimmune thyroid disease; and D, diffuse goiter.
†The reference interval for thyrotropin is 0.4 to 4.0 mU/L.

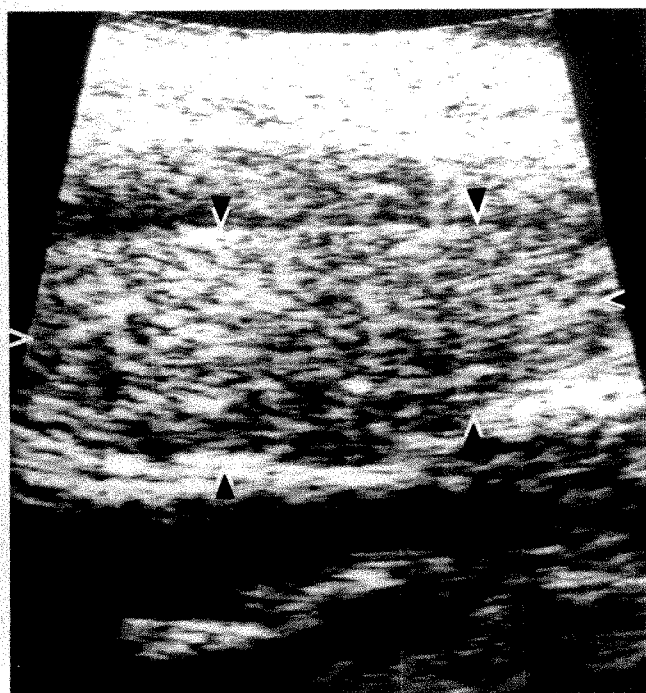


Fig 1.—Longitudinal section of normal thyroid lobe with uniform echo pattern. The arrowheads mark the border of the thyroid lobe.

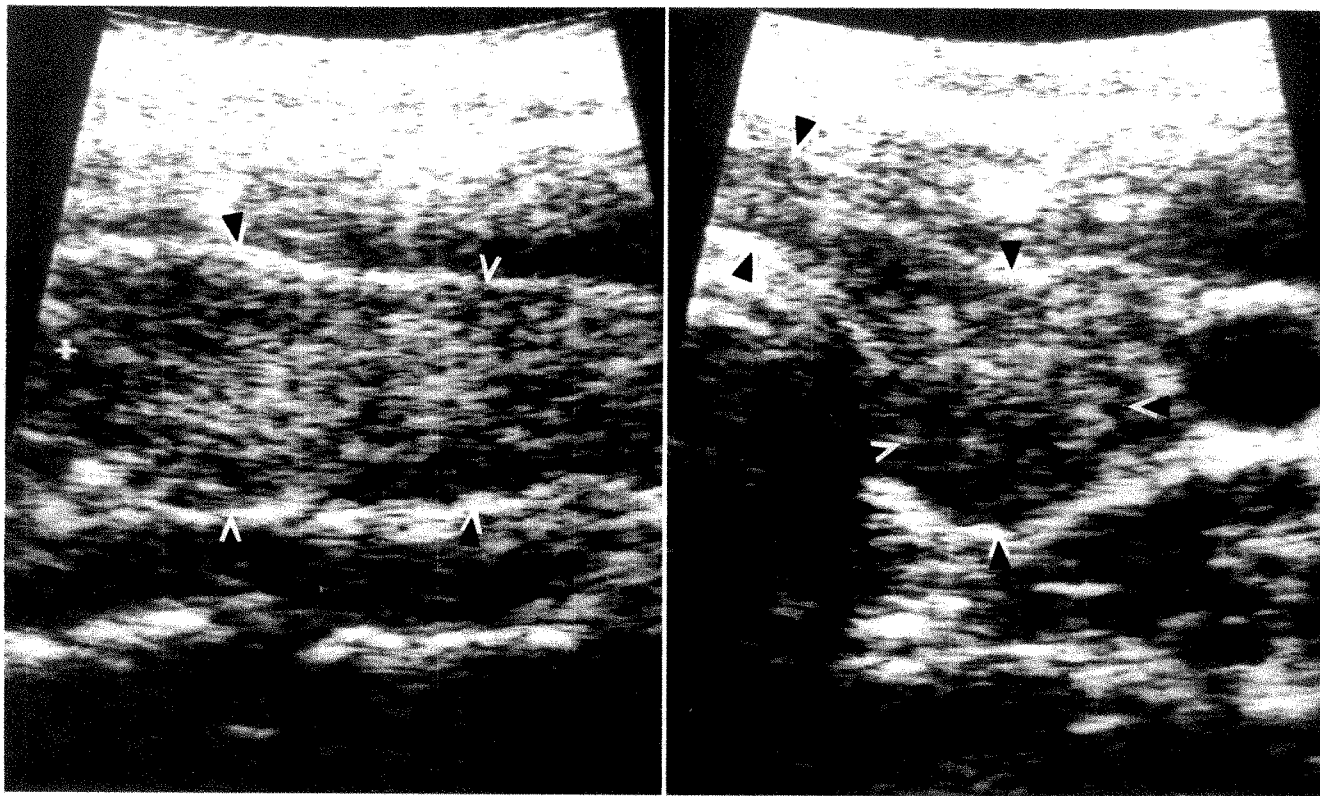


Fig 2.—Longitudinal (left) and cross-sectional (right) scans of thyroid gland. Irregular small areas of decreased echogenicity are seen throughout the gland and are classified as grade 3. The arrowheads mark the border of the thyroid lobe and isthmus.

Fig 3.—Cross-sectional scan of a completely abnormal thyroid gland with apparently no normal parenchyma, classified as grade 4. The arrowheads mark the border of the thyroid lobe and isthmus.

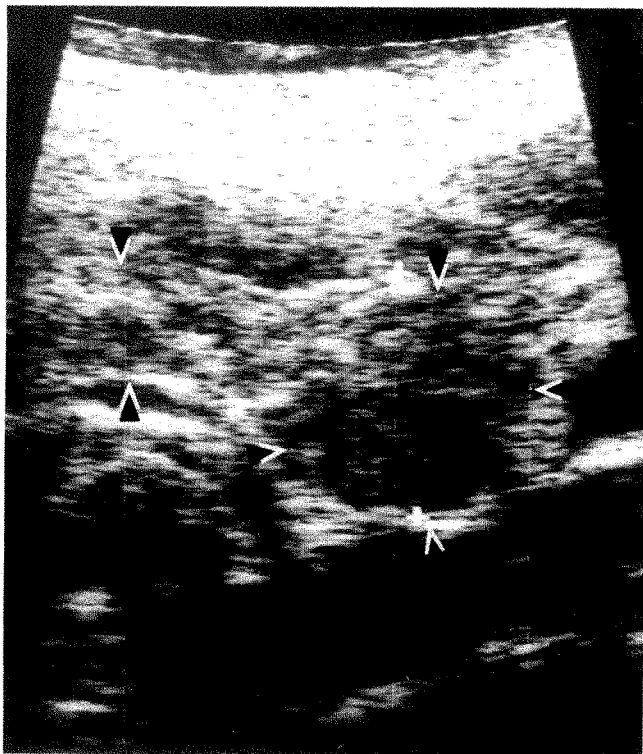


Fig 4.—“Pseudocystic” image concomittant with de Quervain's thyroiditis, classified as grade 4. The arrowheads mark the border of the thyroid lobe and isthmus.



ple enlargement of the thyroid gland with a normal echo pattern; grade 2, small areas with low echo amplitude in some part of the gland; grade 3, small areas of hypoechogenicity throughout the whole thyroid surrounded by some normal echoes (Fig 2); and grade 4, completely abnormal echo pattern with large cystic regions and no apparently normal parenchyma (Fig 3).

There was no correlation between the degree of abnormality on the ultrasound imaging and the Tgab titer. All patients with diffuse colloid goiter on aspiration biopsy cytology had normal echo patterns. The gland of the patient with a granulomatous thyroiditis (de Quervain's thyroiditis) differed in echo pattern from those of the patients with AITD by manifesting a patchy echo pattern with pronounced hypoechogenicity giving a "pseudocystic" image unlike that of normal and solid tissue (Fig 4).

Thyroid Antibody Testing

Thyroglobulin autoantibodies were detected in 9 (90%) of 10 patients with AITD. Two patients with colloid goiter were also Tgab positive, as was the patient with subacute thyroiditis. All 4 patients with uncertain diagnoses were also Tgab positive.

Microsomal antibodies were detected in only 4 (40%) of 10 patients with AITD and in none of the patients with diffuse colloid goiter. Three patients had inconclusive diagnoses.

COMMENT

In the present study, all children with AITD showed abnormalities on ultrasound imaging and manifested comparable patterns of nonhomogeneous hypoechogenicity. The echo pattern differed both from the normal echoes found in the children with colloid goiter and from the multimicrocystic appearance in the patient with granulomatous thyroiditis. In agreement with our results, Pöyhönen and Lenko⁵ found abnormal ultrasound imaging in 92% of their children with AITD, whereas thyroid ultrasound imaging in a retrospective study by Bachrach et al⁶ was found to be of limited value in the differential diagnosis of diffuse thyroid lesions, despite that they identified 47% of the patients with Hashimoto thyroiditis. In contrast to the echo pattern observed in all our patients with AITD, Espinasse¹¹ found a homogeneous micro-echo pat-

tern in a patient with chronic lymphocytic thyroiditis. It is believed that the positive findings on ultrasonic imaging were due to a marked infiltration of inflammatory cells and formation of germinal centers, as these are always very echolucent.¹⁰ Therefore, it is possible that the difference in echo patterns between our patients with AITD and those of Espinasse may be due to differences in the degree and pattern of lymphocytic infiltration and in the degree of fibrosis. There is a correlation between the level of the echo amplitude and the degree of lymphocytic infiltration and fibrosis.⁵ Hayashi et al¹² were able to differentiate severe and less severe cases of thyroiditis according to the echogenicity pattern of the thyroid; they reported that every hypoechogenic area of the thyroid was severely degenerated, with disappearance of the thyroid follicles.

Ultrasonic imaging identified all patients with AITD on aspiration biopsy cytology, whereas thyroid antibody testing identified only 90% (9/10). The failure to detect Tgab in 1 of the patients with AITD may have been due to the formation of circulating immune complex giving false-negative antibody test results. Two patients with colloid goiter (29%) were Tgab positive, which is comparable with the report of Ling et al¹³ in which 2 (25%) of 8 of the subjects with colloid goiter were positive for serum antithyroid antibodies. All 4 patients with uncertain diagnoses also had detectable Tgab. These patients may only have had focal thyroiditis without fibrosis and Tgab was not, therefore, detectable either on ultrasonic imaging or with aspiration biopsy cytology. The patient with both AITD and de Quervain's thyroiditis on aspiration biopsy cytology had Tgab, and, thus, AITD is the most probable diagnosis, though further follow-up of this patient will be required to establish which diagnosis is correct.

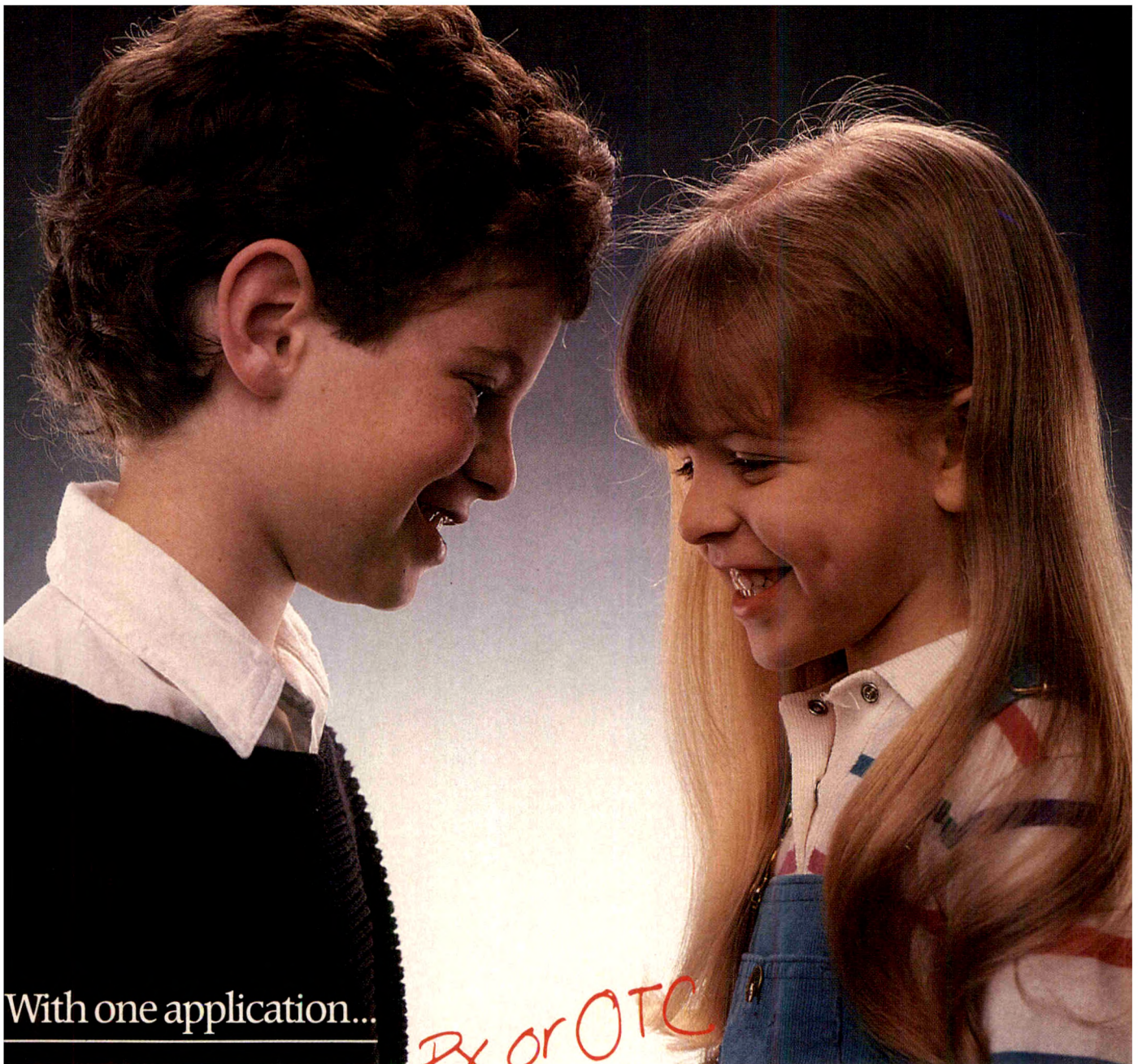
The other patient with de Quervain's thyroiditis also had myasthenia gravis; in this patient, the clinical picture was not typical of de Quervain's thyroiditis, though both the aspiration biopsy cytology and ultrasound findings were. Future clinical observations may provide a clue to these apparently anomalous findings. In seven patients with autoimmune thyroiditis, an ultrasonic examination was repeated 1½ to 2 years after

the first; in five patients the echo pattern had progressed, and in two patients it was unchanged, but in none of them had it improved or normalized, though during thyroxine treatment the gland had decreased in size and was below the normal range.

In conclusion, our study shows that ultrasonic imaging is a valuable method with good diagnostic accuracy in the differential diagnosis of diffuse thyroid disorders. The examination is noninvasive and easy to perform and is well tolerated by children and acceptable to their parents. There are no difficulties in differentiating between diffuse colloid goiter and thyroiditis. Even without great experience, grading is simple and easily performed. Perhaps an ideal diagnostic strategy in pediatrics might be the combination of ultrasonic imaging with the determination of Tgab.

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The best treatment to kill lice and nits

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Clinical studies prove Nix™ kills lice and nits and protects against reinfestation better than a single application of Kwell® and Rid®.* Only Nix

provides 14-day protection against reinfestation—*with one application*—and no evidence of CNS toxicity as reported with lindane overexposure.⁵

More patients lice-free at day 14 with Nix

vs 1% lindane ¹		vs Kwell ²		vs Rid ³	
99%	85%	98%	76%	96%	62%
Nix	lindane	Nix	Kwell	Nix	Rid

Rid labeling requires a second application at 7-10 days. Carson et al demonstrated 100% efficacy for Nix and 93.5% efficacy for Rid when used according to manufacturer's labeling.⁴

Nix FOR LICE
CREME RINSE

permethrin 1%

Call 1-800-FOR-LICE
to report head lice outbreaks



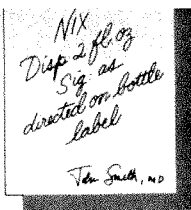
Please see adjacent page for brief summary of prescribing information.

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NIX[®] FOR LICE[®]

CREME RINSE

permethrin 1%



PEDICULICIDAL/OVICIDAL ACTIVITIES: *In vitro* data indicate that permethrin has pediculicidal and ovicidal activity against *Pediculus humanus var. capitis*. The high cure rate (97-99%) of Nix in patients with head lice demonstrated at 14 days following a single application is attributable to a combination of its pediculicidal and ovicidal activities and its residual persistence on the hair which may also prevent reinfestation.

INDICATIONS AND USAGE: Nix is indicated for the single-application treatment of infestation with *Pediculus humanus var. capitis* (the head louse) and its nits (eggs). Retreatment for recurrences is required in less than 1% of patients since the ovicidal activity may be supplemented by residual persistence in the hair. If live lice are observed after at least seven days following the initial application, a second application can be given.

CONTRAINDICATIONS: Nix is contraindicated in patients with known hypersensitivity to any of its components, to any synthetic pyrethroid or pyrethrin, or to chrysanthemums.

WARNING: If hypersensitivity to Nix occurs, discontinue use.

PRECAUTIONS:

General: Head lice infestation is often accompanied by pruritus, erythema, and edema. Treatment with Nix may temporarily exacerbate these conditions.

Information for Patients: Patients with head lice should be advised that itching, redness, or swelling of the scalp may occur after application of Nix. If irritation persists, they should consult their physician. Nix is not irritating to the eyes; however, patients should be advised to avoid contact with eyes during application and to flush with water immediately if Nix gets in the eyes. In order to prevent accidental ingestion by children, the remaining contents of Nix should be discarded after use.

Combing of nits following treatment with Nix is not necessary for effective treatment. However, patients may do so for cosmetic or other reasons. The nits are easily combed from the hair treated with Nix after drying.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Six carcinogenicity bioassays were evaluated with permethrin, three each in rats and mice. No tumorigenicity was seen in the rat studies. However, species-specific increases in pulmonary adenomas, a common benign tumor of mice of high spontaneous background incidence, were seen in the three mouse studies. In one of these studies there was an increased incidence of pulmonary alveolar-cell carcinomas and benign liver adenomas only in female mice when permethrin was given in their food at a concentration of 5000 ppm. Mutagenicity assays, which give useful correlative data for interpreting results from carcinogenicity bioassays in rodents, were negative. Permethrin showed no evidence of mutagenic potential in a battery of *in vitro* and *in vivo* genetic toxicity studies. Permethrin did not have any adverse effect on reproductive function at a dose of 180 mg/kg/day orally in a three-generation rat study.

Pregnancy: Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits (200-400 mg/kg/day orally) and have revealed no evidence of impaired fertility or harm to the fetus due to permethrin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the evidence for tumorigenic potential of permethrin in animal studies, consideration should be given to discontinuing nursing temporarily or withholding the drug while the mother is nursing.

Pediatric Use: Nix is safe and effective in children two years of age and older. Safety and effectiveness in children less than two years of age have not been established.

ADVERSE REACTIONS: The most frequent adverse reaction to Nix is pruritus. This is usually a consequence of head lice infestation itself, but may be temporarily aggravated following treatment with Nix. 5.9% of patients in clinical studies experienced mild temporary itching; 3.4% experienced mild transient burning/stinging, tingling, numbness, or scalp discomfort; and 2.1% experienced mild transient erythema, edema, or rash of the scalp.

DOSAGE AND ADMINISTRATION:

Adults and Children: Nix is intended for use after the hair has been washed with shampoo, rinsed with water and towel dried. Apply a sufficient volume of Nix to saturate the hair and scalp (especially behind the ears and on nape of the neck). Nix should remain on the hair for 10 minutes before being rinsed off with water. A single treatment is sufficient to eliminate head lice infestation. Combing of nits is not required for therapeutic efficacy, but may be done for cosmetic reasons or to meet school "no nit" policies. A nit comb is provided.

SHAKE WELL BEFORE USING.

HOW SUPPLIED: Nix (Permethrin) 1% (wt./wt.) Creme Rinse is supplied in plastic squeeze bottles that contain 2 fl. oz. weighing 56 g. (NDC-0081-0780-81)

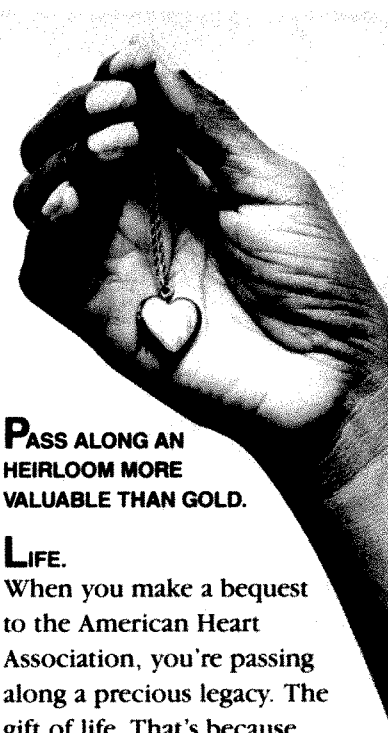
Store at 15°-25°C (59°-77°F).

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Cost per word	\$1.75	\$1.60
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Professional Opportunities

FLORIDA — Seeking board-certified/board-eligible pediatrician to join busy solo pediatric practice on sunny west coast of Florida. Salaried position for one year leading to partnership. Please contact: D. French, MD, 1305-F South Fort Harrison, Clearwater, FL 34616. (813) 446-1161.

BOARD-CERTIFIED/-ELIGIBLE PEDIATRICIAN to join our 25-physician, multi-specialty group practice. All practice costs paid, full range of benefits and early partnership status. Experience our family-oriented community with its unsurpassed scenic beauty and outdoor recreational opportunities, situated midpoint between metropolitan Seattle and Vancouver, British Columbia. Contact: Shane Spray, 1400 East Kincaid Street, Mount Vernon, WA 98273. (206) 428-2524.

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CALIFORNIA — PEDIATRIC INTENSIVIST to join progressive 13-bed PICU at Huntington Memorial Hospital in Pasadena, California, a major affiliate of the University of Southern California. Excellent salary, bonus and partnership opportunities. Persons with pulmonary training are encouraged to inquire. Inquiries to: Edgardo L. Arcinue, MD, Director, PICU, Huntington Memorial Hospital, 100 Congress Street, Pasadena, CA 91105. (818) 397-8688.

PEDIATRICIAN: BEMIDJI CLINIC MERITCARE is seeking a second BC/BE pediatrician to join an expanding 25-physician multi-specialty group. The local Level II hospital has 800+ deliveries per year and is affiliated with a tertiary care center with a NACHRI designated children's hospital. The area offers a wide range of recreational opportunities. Guaranteed first year salary with rewarding long term compensatory arrangements. Respond to: Robert C. Montgomery, MD, Physician Recruitment Chairman, Fargo Clinic MeritCare, 737 Broadway, Fargo, ND 58102. (800) 437-4010.

LINCOLN, NEBRASKA — BC/BE pediatrician to join three other pediatricians in a busy multi-specialty group. Available immediately, take over existing practice of retiring doctor. City of 150,000 has good schools and safe family environment. Good opportunity for professional growth. Competitive salary and benefits. Send CV to: R.Z. Gallion, P.O. Box 81009, Lincoln, NE 68501.

THREE PEDIATRICIANS SEEKING FOURTH for growing practice in 61-physician multi-specialty group in city of 10,000, 40 miles south of Madison. Attractive salary and benefits. Contact: James Raettig, MD, The Monroe Clinic, Monroe, WI 53566. (608) 328-7214.

PEDIATRICIAN will be welcomed to Oswego, New York, a 60,000 population primary service area. A college town located on Lake Ontario, 40 miles north of Syracuse. Exceptional educational, cultural and recreational activities, including salmon fishing. Contact: Garo Taft, MD, 110 West Sixth Street, Oswego, NY 13126. (315) 349-5526.

TEXAS — PEDIATRICIAN. A pediatrician is needed to establish practice in conjunction with the recruitment of a neonatologist, in College Station, Texas, the home of Texas A&M University. Financial assistance with possible future group association. Send your CV to: Professional Relations, Department ADC-9C, P.O. Box 1438, Louisville, KY 40201-1438.

Professional Opportunities

FLORIDA EAST COAST — PEDIATRICIAN. An outstanding opportunity for a BC/BE pediatrician to join one of two well-established and very busy pediatric groups located along the east coast of Florida. Attractive financial package with early partnership is offered. For further information send your CV to: John Hollander, Professional Relations, Humana Inc., Department ADC-9D, 500 West Main Street, Louisville, KY 40201-1438. Or call toll-free: (800) 626-1590.

CAMP DOCTORS — Boys' summer camp in Maine. Two week minimum stay preferred. Camp Cedar, 1758 Beacon Street, Brookline, MA 02146. (617) 277-8080.

WASHINGTON — BC/BE pediatrician to join one pediatrician in busy general pediatric practice at multi-specialty clinic; excellent facilities at both clinic and hospital. Excellent salary and benefits. Prime outdoor recreational area. Contact: Terry Coplin, 840 Hill Avenue, Moses Lake, WA 98801.

SOUTHERN CALIFORNIA — PEDIATRICIAN. A board-certified pediatrician, practicing in the San Fernando Valley for the past 10 years, is now seeking an associate. This is one of the busiest practices in the area. For further information send CV to: Manager, Professional Relations, Department ADC-9B, P.O. Box 1438, Louisville, KY 40201-1438. Or call toll-free: (800) 626-1590.

PEDIATRICIAN

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OR

James Russell
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PEDIATRICIANS — Southeast United States: Several progressive groups seeking board-certified or board-eligible pediatricians. Send CV to: CPR Associates, P.O. Box 235005, Montgomery, AL 36123-5005.

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Interested candidates should send their curriculum vitae and supporting documents to:

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We have other Pediatric opportunities not listed here.

For further information, call TOLL-FREE 1-800-626-1590, or send your curriculum vitae to: Manager, Professional Relations, Humana Inc., Dept. ADC-9, 500 West Main Street, Louisville, KY 40201-1438.

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PEDIATRICIAN — Seeking a pediatrician to assume a 30 year, private practice upon my retirement on June 30, 1990. Group coverage available. Located 15 minutes from university, state and county hospitals in a suburban community of southern New England. Ideal for a family with children. Private and public schools nearby. Wide variety of recreational and cultural activities. Close to major metropolitan areas. Contact: Sophie M. Wlassich, MD, 821 Post Road, Warwick, RI 02888. (401) 781-2090.

WESTERN STATES — BE/BC pediatricians for multi-specialty clinics, hospitals. Also, private California practices for sale. Call/send CV: Bradshaw Associates, 21 Altamont, Orinda, CA 94563. (415) 376-0762.

PEDIATRICIAN needed for rapid growth area. 119-bed, rural hospital located between Nashville, Tennessee and Huntsville, Alabama. Substantial monthly salary guarantee plus a quiet lifestyle in a beautiful country setting. Contact: Doug Dailey, Lewisburg Community Hospital, P.O. Box 1609, Lewisburg, TN 37091. (615) 359-6241.

BOARD-CERTIFIED/-ELIGIBLE PEDIATRICIAN for a position in 11-person, multi-specialty pediatric department at 175-bed (2,700 deliveries/year) state hospital. Specialty training or interest in nephrology, endocrinology, pulmonary or infectious diseases preferred but not essential. Responsibilities include primary patient care and teaching of medical students and houseofficers. All applicants must have skills in the resuscitation and stabilization of critically ill children, infants and newborns. For further information, please send CV to: Dr. Richard Howes, MD, University Medical Center, 2390 West Congress Street, Lafayette, LA 70506. LSUMC is an AA/EO employer.

BC/BE PEDIATRICIAN needed immediately to join four-member pediatric department of 100-member, multi-specialty clinic with 26 satellite locations. Metropolitan population of approximately 150,000 and university affiliation. Contact: T. Mausbach, MD, Dakota Clinic, Ltd., P.O. Box 6001, Fargo, ND 58108. (701) 280-3346.

BC/BE PEDIATRICIAN sought for community of Clovis, New Mexico. Financial package available for this private practice opportunity. Please send CV to: Bill Norris, Physician Recruiter, SCHS, P.O. Box 26666, Albuquerque, NM 87125.

BC/BE PEDIATRICIAN to join thriving practice in Jacksonville, Florida suburb. Competitive salary plus incentives and partnership opportunity including building ownership. Liberal time off and excellent benefits. Send CV to: Mark Goldschmidt, MD, 1409 Kingsley Avenue, Suite 9-G, Orange Park, FL 32073.

MASSACHUSETTS — Two BC pediatricians seeking one or two BC/BE pediatricians. Southeastern Massachusetts coastal community. Easy access to Boston and Providence. Rapidly growing practice and good hospital, recreation, spouse job opportunities, schools. Send CV: Dr. J. Conway and Dr. S. Rogers, 53 Marion Road, Wareham, MA 02571.

TEXAS — **PEDIATRICIAN**. Unique opportunity for a pediatrician in offices next to our new replacement hospital in the high-growth section of Abilene, Texas. Immediate referrals and attractive financial assistance. Abilene, located 150 miles west of Dallas/Ft. Worth, is the heart of a 22-county trade area and is home to three universities and Dyess AFB. Send CV to: Manager, Professional Relations, Humana Inc., Department ADC-11, 500 West Main Street, Louisville, KY 40201-1438. Or call toll-free: (800) 626-1590.

UTAH — Pediatrician to replace fourth pediatrician, who is retiring, in multi-specialty clinic. Shared call. Happy group. Guaranteed salary. University, mountain recreation, skiing. Contact: Neal J. Byington, 225 East 400 North, Logan, UT 84321. (801) 752-0422.

ALABAMA/FLORIDA AREA — Looking for security? Want to be your own boss? BC/BE pediatrician needed for a 70-bed hospital position. \$90,000 salary plus benefits. Send CV to: HQS, 6053 Tammy Drive, Alexandria, VA 22310; or call: (800) 359-1666.

PEDIATRICIAN — Southeastern Oklahoma, 90 miles to Dallas, near beautiful Lake Texoma. Modern general acute care, 100-bed facility, opened in 1987. One other pediatrician and two OB/GYNs in this community of 14,000. This opportunity is available in a university town, offering cultural and sporting events as well as an excellent school system. Reply to: Tom Rozewicz, Medical Center of Southeastern Oklahoma, 1800 University Drive, Durant, OK 74701. (405) 924-3080.

COLORADO — BC/BE pediatrician to join well-established, two-person practice. Active Level II nursery. Reply to: Richard Booth, MD, 1148 East Elizabeth, Fort Collins, CO 80524. (303) 484-4871.

MOUNTAIN STATES COMMUNITIES need pediatricians. Smaller communities with excellent incentive packages and referral bases. All close to mountain recreation. Call Rita Longino at (505) 262-1871; or send CV to: Excel of Albuquerque, 1717 Louisiana NE, Suite 218, Albuquerque, NM 87110.

NEONATOLOGIST — The Department of Pediatrics, William Beaumont Hospital is seeking a full-time, academically-oriented neonatologist to join our Division of Newborn Medicine. The position involves clinical care, teaching and research. We are interested in recruiting somebody with demonstrated capability and interest in clinical and/or basic research, as well as proficiency in teaching residents. Interested individuals should submit their CV to: Daniel Batton, MD, Chief, Division of Newborn Medicine; or M. Jeffrey Maisels, MD, Chairman, Department of Pediatrics, William Beaumont Hospital, 3601 West Thirteen Mile Road, Royal Oak, MI 48072.

NORTHERN CALIFORNIA — The Permanente Medical Group is currently seeking a BC/BE pediatrician to join our congenial 17-physician Pediatric Department in the Roseville facility. This family-oriented community has much to offer, including affordable housing. Outpatient clinic is located twelve miles from the Sacramento Medical Center. Members of our large, multi-specialty group earn highly competitive compensation and outstanding benefits including malpractice insurance, medical, dental and group life insurance, vacation, educational leave, an excellent retirement program and special arrangements for physicians transferring from established practice. For more information, please send CV to: Dr. Makol, The Permanente Medical Group, Inc., 1001 Riverside Avenue, Roseville, CA 95678.

PEDIATRICS, PRIMARY CARE — Excellent practice opportunity available for a BC/BE pediatrician to practice at Burbank Hospital, a progressive 200+ bed community hospital located in north central Massachusetts (Fitchburg). Medical/dental staff includes 150 physicians and a service area population of 150,000. Strong obstetrics group affiliated with the hospital (births have increased 40% over four years to 1,100). Community is strong on family values and physician loyalty. Hospital maintains physician referral service. Assistance is available to help you in establishing a private practice. Please reply with letter and CV to: Douglas D. Byrd, Director, Burbank Hospital, Fitchburg, MA 01420.

AUGUSTA, GEORGIA — Physicians' Multispecialty Group is seeking a second BC/BE pediatrician to join an expanding nine-physician group. Excellent salary, fringe benefits and paid vacation. Experience and/or interest in intensive care a must. Respond to: PMG, P.O. Box 3726, Augusta, GA 30914-3726.

PLEASE NOTE — Address replies to box number ads as follows: Box number, _____, c/o AJDC, P.O. Box 1510, Clearwater, FL 34617.

Professional Opportunities

THE DEPARTMENT OF PEDIATRICS at William Beaumont Hospital is seeking a qualified pediatrician for the position of Director, Division of Pediatric Infectious Disease. William Beaumont Hospital is a 934-bed general hospital located thirteen miles north of Detroit in Royal Oak, Michigan. We have 60 general pediatric beds, a 30-bed NICU and 6,000 deliveries annually. Our department has a staff of 120 pediatricians and 20 full-time pediatric subspecialists. There are some 4,000 admissions annually to our general pediatric floor and 20,000 pediatric visits to the emergency center and outpatient clinics. We are a teaching hospital with independent residency programs in pediatrics and medicine-pediatrics, affiliated with the University of Michigan and Wayne State University. Interested candidates should call or submit their curriculum vitae to: M. Jeffrey Maisels, MD, Chairman, Department of Pediatrics, William Beaumont Hospital, 3601 West Thirteen Mile Road, Royal Oak, MI 48072. (313) 551-0412.

NEW YORK, NEONATOLOGIST—Department of pediatrics, State University of New York at Buffalo/Children's Hospital is seeking faculty member to join eight-member division of neonatology. Assistant or associate professor level. BC in pediatrics, BC/BE in neonatology. Division conducts NIH-sponsored laboratory research on perinatal pulmonary and circulatory physiology and clinical research in pulmonary physiology, immunology and gastroenterology, including five years experience with surfactant therapy. CV to: Frederick C. Monn, MD, Chief, Division of Neonatology, Children's Hospital, 219 Bryant Street, Buffalo, NY 14222. Affirmative action/equal opportunity employers.

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Professional Opportunities

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TENNESSEE — General pediatrician. Fifth pediatrician BC/BE needed for very well-established group practice. Care includes newborn with Level II nursery through late adolescence. Hospital is 650-bed tertiary care facility. City of 50,000 with medical drawing area of 450,000. Located on major interstate 75 miles from Memphis, and 120 miles from Nashville. Good schools, sports, local symphony. Salary guarantee with partnership after 1-2 years. Opportunity to take part in teaching FP residents University of Tennessee. Good call schedule with generous vacation and meeting time. Please reply with CV to: Jim Levernier, MD, The Children's Clinic, PA, 804 North Parkway, Jackson, TN 38305.

THE DEPARTMENT OF PEDIATRICS, University of Pittsburgh School of Medicine seeks a BC/BE developmental/behavioral pediatrician for the Child Development Unit of Children's Hospital of Pittsburgh. This tenure track position has excellent opportunities for program development, clinical and/or basic research, education of medical students and pediatric housestaff, and direct clinical care. Candidate must have experience in research and in clinical service with handicapped or at risk children. Salary and starting date are negotiable. Send letter of interest, CV and three letters of reference to: Heidi Feldman, MD, PhD, Director, Child Development Unit, Children's Hospital of Pittsburgh, 3705 Fifth Avenue, Pittsburgh, PA 15213-2583. An equal opportunity employer.

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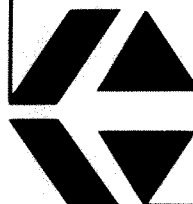
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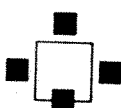
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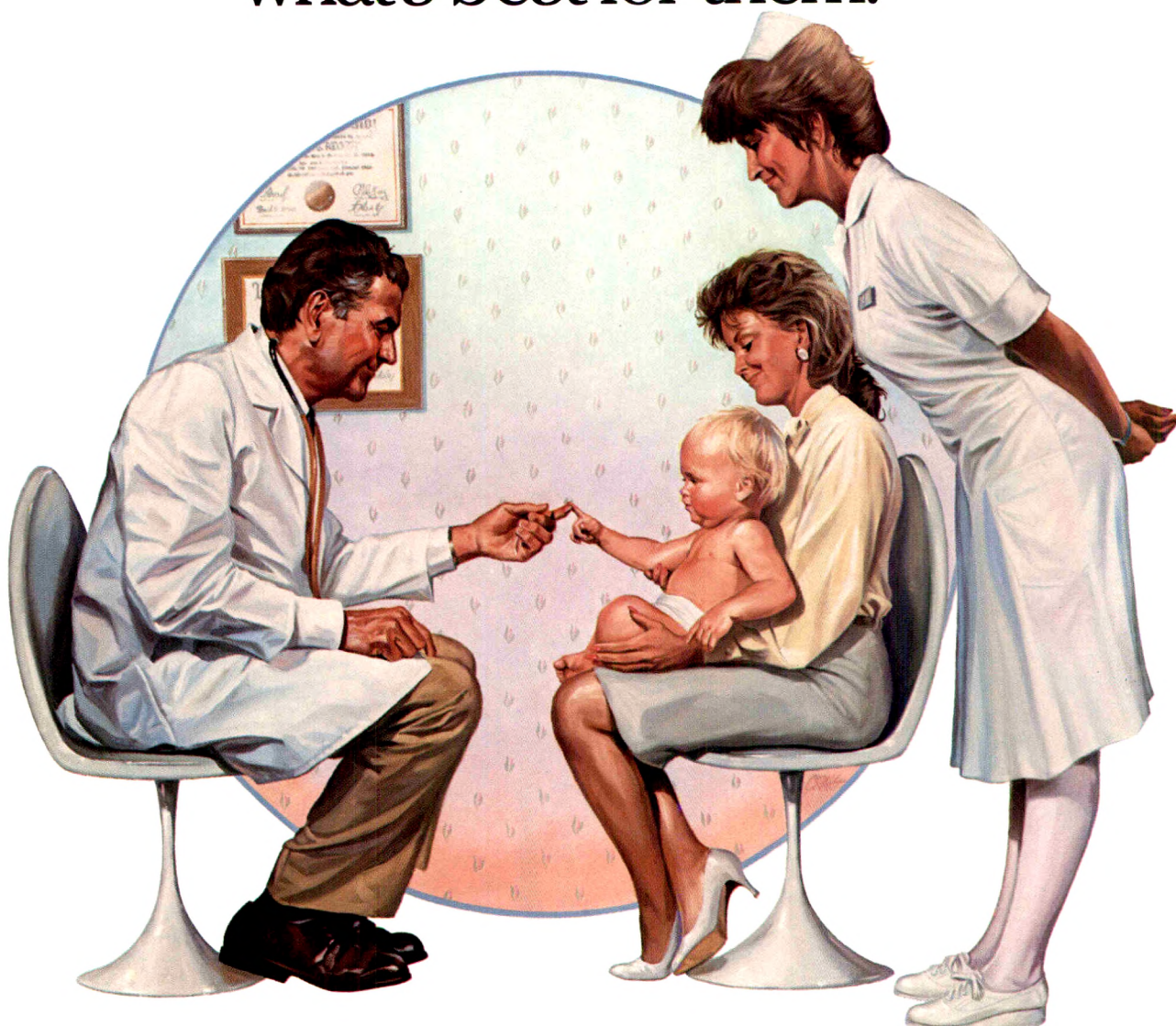
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... on the consumer promotion of infant formula.

There is a development that undermines your control over the infant's diet and health, and that undermines breastfeeding—the advertisement of formulas directly to the mother through TV, magazines and mail.

On June 1, the President of the American Academy of Pediatrics sent a letter to all Fellows of the Academy reaffirming its stance against consumer advertising, and expressing concern that other formula companies might follow Nestlé/Carnation.

This concern was justified. On June 15, it was announced at a press conference that Mead Johnson/Bristol-Myers will be producing an infant formula to be sold and marketed under the Gerber label. Part of the program is a multimillion-dollar budget for advertising the formula directly to mothers via TV and print.

Speaking at the press conference, Gerber Products Division President Robert L. Johnston, Jr., said that Gerber was entering the market because it had, "identified significant changes in usage that convinced us the timing was right...."

"First," he said, "there is a rapid decline in breast-feeding after mothers leave the hospital." And, "... parent decision regarding baby formula brand selection has grown...."

The irony is inescapable and appalling. In other words, because breastfeeding is declining, more infant formulas should be promoted to the mother. In other words, because some mothers are making feeding decisions on their own, even more mothers should follow suit.

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The JOURNAL is meant to provide physicians in all specialties who practice pediatric medicine a complete and accurate synthesis of all current research developments and clinical topics pertinent to their practice, as well as an open forum for dialogue on scientific, educational, ethical, and humanistic issues of concern to any intellectual committed to the practice of pediatrics.

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Step 1.—Cover Letter.—All manuscripts must be accompanied on submission by a cover letter giving the name, address, affiliation, and telephone number of the corresponding author. The letter must include ALL of the following statements SIGNED BY ALL AUTHORS (ORIGINAL SIGNATURES):

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Step 2.—Manuscript Format.—All articles submitted should have the following features:

1. Four copies of the manuscript should be submitted; three are for transmission to referees and one is to be retained in the editorial office. We prefer an original and three copies.

2. Manuscripts should be typed in triple-spaced format on heavy-duty white bond paper, 21.6×27.9 cm (8½×11 in) with 2.5-cm (1-in) margins. Do not use justified right margins.

3. Title should be no more than 75 characters.

4. Authors should be limited to six, all of whom have contributed to the study and manuscript preparation, are familiar with its substance, and are able to defend its conclusions.

5. The title page should give full names, degrees, and academic affiliations of all authors, address for request of reprints, and, if the manuscript was presented at a meeting, the organization, place, and exact date on which it was read.

6. Writing style should conform to proper English usage and syntax; consult the *American Medical Association Manual of Style*, available from Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202.

7. Abstract should be limited to 135 words or less.

8. Each table should be typed, with a title, on a separate sheet of paper, with each line, including headings, double-spaced. Continuations should be on a second sheet with all headings repeated.

9. Use Système International (SI) measurements throughout the manuscript.

10. Illustrations should be high-contrast, glossy prints, in quadruplicate, unmounted and untrimmed; lettering should be legible after reduction to column size. Figure number, name of first author, and arrow indicating “top” should be typed on a gummed label and affixed on the back of each illustration. Do not write directly on the print.

Magnification and stain should be provided for histologic sections. Full-color illustrations should be submitted as 35-mm, positive color transparencies, mounted in cardboard and carefully packaged. Do not submit glass-

fee must accompany submission.

All photographs in which there is a possibility of patient identification should be accompanied by a signed statement of consent from both parents (or guardians). Covering eyes to mask identity is not sufficient.

11. References should be listed in order of their appearance in the text, type double-spaced, and in AMA format. Please follow the exact order of information and punctuation in the examples below. Note: List all authors and/or editors up to six; if more than six, list the first three and “et al.”

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Books: Naeye RL. How and when does antenatal hypoxia damage fetal brains? In: Kubli F, Patel N, Schmidt W, Linderkamp O, eds. *Perinatal Events and Brain Damage in Surviving Children*. New York, NY: Springer Verlag NY Inc; 1988:83-91.

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Authors are responsible for the accuracy of the references.

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Step 3.—Special Departments.—Criteria for several special departments are given below.

1. *The Pediatric Forum.*—This is the place for comment, criticism, observations, and discussion of “issues of current concern and importance for children's health,” in addition to letters that comment on articles in previous issues of *AJDC*. The Editor reserves the right to conduct review of and to edit all submissions. THE READER SHOULD SUBMIT TRIPLE-SPACED COPY CLEARLY MARKED “FOR PUBLICATION” AND SIGNED BY ALL AUTHORS. REFERENCES, IF INCLUDED, SHOULD CONFORM TO THE USUAL AMA FORMAT. Copyright assignment, signed by all authors, must accompany the original submission.

2. *From Research to Relevance.*—PURPOSE: To focus on significant research that has a high probability of being translated into clinical usefulness.

3. *Educational Interventions.*—PURPOSE: To share information concerning any educational efforts in the broad field of pediatrics.

4. *Sports Medicine.*—PURPOSE: To provide current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention, diagnosis, and treatment of sports-related illnesses and injuries.

5. *Picture of the Month.*—Submissions should be sent directly to Murray Feingold, MD, National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135, and should conform to the format for original articles in terms of the text, references, and illustrations.

6. *Radiological Case of the Month.*—Submissions should be sent directly to Beverly P. Wood, MD, University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Submissions should conform to the format for original articles in terms of the text, references, and illustrations.

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- ____ 1. Cover letter with name, address, and telephone number of corresponding author.
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PRECAUTIONS: General—Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions that augment systemic absorption include application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.

Therefore, patients receiving a large dose of any potent topical steroid applied to a large surface area should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests, and for impairment of thermal homeostasis. If HPA axis suppression or elevation of the body temperature occurs, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function and thermal homeostasis are generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity (see PRECAUTIONS, Pediatric Use).

If irritation or hypersensitivity develops with the combination nystatin and triamcinolone acetonide, treatment should be discontinued and appropriate therapy instituted.

The treated skin area should not be bandaged or otherwise covered or wrapped as to be occluded.

Laboratory Tests—If there is a lack of therapeutic response, appropriate microbiological studies (e.g., KOH smears and/or cultures) should be repeated to confirm the diagnosis and rule out other pathogens, before instituting another course of therapy.

A urinary free cortisol test and ACTH stimulation test may be helpful in evaluating hypothalamic-pituitary-adrenal (HPA) axis suppression due to corticosteroid.

Carcinogenesis, Mutagenesis, and Impairment of Fertility—Long-term animal studies have not been performed to evaluate carcinogenic or mutagenic potential, or possible impairment of fertility in males or females.

Pregnancy Category C—There are no teratogenic studies with combined nystatin and triamcinolone acetonide. Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. Therefore, any topical corticosteroid preparation should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Topical preparations containing corticosteroids should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers—It is not known whether any component of this preparation is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised during use of this preparation by a nursing woman.

cream formulation on a limited number of pediatric patients ranging in age from two months through 12 years, the combination cleared or significantly ameliorated the disease state in most patients.

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced hypothalamic-pituitary-adrenal (HPA) axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.

HPA axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.

ADVERSE REACTIONS: Acneiform eruption has been reported to occur in approximately one percent of patients with use of combined nystatin and triamcinolone acetonide.

Nystatin is virtually nontoxic and nonsensitizing and is well tolerated by all age groups, even during prolonged use. Rarely, irritation may occur.

The following local adverse reactions are reported infrequently with topical corticosteroids (reactions are listed in an approximate decreasing order of occurrence): burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.

Patients should report any signs of local adverse reactions.

OVERDOSAGE: Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS, General); however, acute overdosage and serious adverse effects with dermatologic use are unlikely.

J4-019B/J4-110

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CONTRAINDICATIONS

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PRECAUTIONS

Should a reaction of hypersensitivity occur the drug should be immediately withdrawn and appropriate measures taken.

These preparations are not for ophthalmic use.

ADVERSE REACTIONS

Nystatin is virtually nontoxic and nonsensitizing and is well tolerated by all age groups including debilitated infants, even on prolonged administration. If irritation on topical application should occur, discontinue medication.

(J3-327C)

The Pediatric Forum

This department of AJDC is reserved for comment, criticism, observation, and discussion of "issues of current concern and importance for children's health." The Editor encourages our readers to express themselves on a variety of topics and issues. Further, we encourage the submission of unique and brief clinical and scientific observations that do not fulfill the criteria for original articles.

A 1-Month Elective in International Health for Senior Pediatric Residents

Sir.—During the past 10 years the number of inquiries concerning the availability of electives in international health from applicants to the pediatric program at the University of Arizona, Tucson, has been steadily increasing. A review of the personal statements of resident applications for 1989-1990 revealed that 20% (18/91) of the candidates had already had experience in international health, another 7% (7/91) will have had international health experience by the time they start their residency, and 3% (3/91) expressed an interest in international health work. This represents a total of 31% (28/91) of this year's applicants. This may, of course, be a biased sample since resident interest in international health may preferentially apply to our program. At least 10% of each class of graduating medical students at our institution have had international health experience. This has prompted the creation of an elective in international health to provide senior pediatric residents the opportunity to validate the depth of their interest. The purpose of this report is to outline how this elective program was implemented, describe its curriculum, and relate 3 years of experience with it.

Implementation.—There are two major obstacles in starting an elective in international health. One relates to establishing contact with a pediatric department in another country and being assured that the experience will be worthwhile. In our department, this was overcome by an association one of our faculty members (B.D.) had maintained with Project HOPE. Through that contact, the pediatric department of the teaching hospital in Tegucigalpa, Honduras, was identified as a possible location for a 1-month elective program for our residents who were fluent in Spanish. Project HOPE had a program in Honduras, and its director was very cooperative in assisting with the development of the program. A visit was made to the proposed site by one of us (B.D.) to

give some lectures, to work with the faculty and house staff, and to ascertain the feasibility of establishing an elective there.

The faculty in Tegucigalpa is well trained. There are more than 200 pediatric beds for infants and children who have an array of common and not-so-common diseases. There is a separate large ward for patients with meningitis, an orthopedic unit for those with acute and chronic osteomyelitis, a rheumatic fever ward, an oral rehydration unit, a large ward for children with pneumonia, a newly opened oncology/hematology ward filled with children with lymphomas and retinoblastomas in various stages and an occasional child with histiocytosis X, and a large malnutrition unit for infants and children with marasmus and kwashiorkor. In addition, there are many children with the tropical diseases endemic to this Central American country, such as cutaneous leishmaniasis and kala-azar, neonatal tetanus, congenital syphilis, intestinal parasites, and cutaneous amebiasis.

Physicians in an extremely busy emergency department see 150 000 children each year, some of whom receive further care in a large holding area. The laboratory and roentgenographic facilities are adequate. The residency program produces graduates with extensive clinical experience, who, during their training, must learn to evaluate and quickly treat numerous sick children using the basic tools of history taking and physical examination rather than relying heavily on the laboratory. This hospital, staffed by a very well-trained faculty and interested and enthusiastic residents, seemed like an ideal setting to initiate our elective in international health.

To increase the benefits to the Honduran pediatricians, the chairman of their department suggested that we send representatives from our faculty who would stay for 2 weeks during the month that our resident was there. Our faculty members would give lectures, make rounds with the Honduran faculty, and assist with the implementation of new procedures, the organization of treatment protocols, and other needs expressed by the host faculty. Several specialty areas that the chairman felt were of highest priority were chosen, and it was within those areas that we would send the appropriate faculty. Project HOPE played a vital role in the initial contact and has continued to assist with that aspect of the program.

We have since established elective alternatives in two English-speaking countries, Jamaica and the Philippines, for our non-Spanish-speaking residents. Those contacts were made through faculty members who were familiar with a particular program abroad. There are a number of US-based voluntary health organizations that may be helpful to other residency programs that are interested in establishing such an elective. Another possibility for establishing contact is through the American Academy of Pediatrics, which is encouraging linkages between state chapters and pediatric societies in developing countries.

The second barrier to starting a program is funding. We were fortunate in that Project HOPE was willing to provide partial support for the program in Honduras. Our electives in the Philippines and Jamaica have been developed with a small departmental subsidy and the philosophy that residents who are truly interested will find monies to cover a portion of their travel and all of their living expenses. Housing accommodations have been obtained with families or within hospital facilities. Such living arrangements have added to the acculturation process of our residents.

Curriculum.—The objectives of this elective program are (1) to give the residents the opportunity to test the depth of their interest in international health as a career option; (2) to see how pediatrics is practiced where resources are scarce; (3) to learn about the health needs and the care that are available for a very large segment of the world's population; (4) to improve basic skills of history taking and physical examination to make diagnoses and commence treatment without the use of sophisticated laboratory tests; (5) to see a large variety of conditions not extensively seen in the United States in a relatively short time, with emphasis on infectious diseases and malnutrition; and (6) to see the application of primary health care in economically depressed urban and/or rural areas and the impact of the Revolution for Child Health as directed by United Nations Children's Fund and the World Health Organization.

In Honduras, our residents spend the majority of the month in the emergency department/holding area of the only tertiary hospital in a country of 3 million people, half of whom are less than 15 years of age. The experience emphasizes acute emergency and stabilization care. In Jamaica,

the month is primarily spent in the pediatric wards of the University of the West Indies. In Manila, the resident's time is divided between the busy ambulatory clinics at the University of Santos Tomas, the Infectious Disease Hospital, and the depressed poverty-ridden areas in and around Manila. There, the residents observe and assist community health workers providing primary health care to their own community neighbors who have had limited education. The essence of that approach is the orientation and application of simple, low-cost, low-technology strategies to improve the health of children.

Selecting the appropriate sites for establishing an elective program should ensure that the conscientious house officer will achieve the defined objectives. The evaluation of our residents was, by necessity, given to the chairman of the department of pediatrics in the host country.

Experience With the Program.—During the inaugural year of the Honduras program, two elective month rotations were available and 1 resident selected this rotation. The enthusiastic message with which she returned was vital in promoting and expanding the elective to six rotations per year and in encouraging other residents to select this elective. In this, the third year of the program, 4 of our 10 senior pediatric house officers have requested the rotation. In 1 month's time in the emergency department/holding area in Tegucigalpa, residents are exposed to a greater variety of acute and serious illnesses than they may see in an entire year in many pediatric programs in the United States. The comments of one of our residents reflects the experiences of all of the residents who have selected this elective:

There was a steady influx of patients with an incredible spectrum of disease waiting outside the emergency room door. Against a background of the ordinary—trauma, dehydration, sepsis, meningitis, pneumonia—came the unusual: neonatal tetanus, tuberculosis, meningitis, snakebite, organophosphate poisoning, kala-azar, infantile spasms, osteogenesis imperfecta, gonococcal conjunctivitis, schizophrenia, encephalocoele, and neonatal AIDS [acquired immunodeficiency syndrome]. The severity of disease was magnified by underlying severe malnutrition and by the long distances which separate the indigent patients from available health care. I remember the quiet, intelligent twelve-year old boy with rheumatic heart disease who presented in severe congestive heart failure which was no longer medically manageable. On his third hospital day his condition was stable, though unimproved, and he seemed unusually quiet. He had come to the hospital alone on the bus, as his family couldn't afford to join him. He died alone that night.

The exchanges our residents have with their Honduran counterparts are reported to be of mutual benefit. Their residents, unable to obtain the most recent journals

or tests, learn some new pathophysiologic concepts, diagnostic approaches, and therapies. Our residents learn that good medical care can be practiced without ordering large numbers of laboratory tests. They return with the concept that the foundation of the art of medicine is complete and detailed history and the performance of a thorough physical examination followed by a thoughtful assessment of the problem, rather than examining computerized printouts of laboratory tests. The faculty has returned with equal enthusiasm, and several are in the process of initiating collaborative research projects with newly found Third-World colleagues.

Those who elect the experience in the Philippines return with some of the same feelings, but they have also been exposed to primary health care as provided in very depressed urban and rural areas. They have seen small groups of neighborhood mothers gathered in tiny living rooms being taught the basis of the United Nations Children's Fund Revolution for Child Health: teaching and supporting traditional health care workers and mothers in the use of low-cost, low-technology strategies to reduce childhood morbidity and mortality. These strategies are exemplified in the acronym GOBI-FFF for growth monitoring, oral rehydration, breast-feeding, immunizations, female education, food supplementation during pregnancy, and family planning.

In Jamaica, our residents learn the management of malnourished infants where Cicely Williams and Derrick Jelliffe did some of their research.¹⁻⁵ They are exposed to illnesses and conditions of Third-World countries but with treatment modalities of those problems provided in a fairly sophisticated setting.

Thus, each experience gives the house officer a view of medicine as practiced in a developing country—a view that serves to broaden their perspectives beyond the confines of life in an academic institution in a developed country, and into a scene that is the norm for a major part of the world.

Conclusions.—We conclude the following regarding our experience with International Health:

1. A variety of electives allow residents the opportunity to explore career options and test the depth of their interest in a variety of areas and disciplines. It is our feeling that this elective program has enhanced the pediatric residency program at the University of Arizona. This current year, the third year since its inception, 4 of the 10 senior house officers have chosen this rotation.

2. The international health elective has provided the resident with the opportunity to learn pediatrics in another setting where the basic skills of history taking and physical examina-

tion are paramount and the laboratory plays only a secondary role; a setting where issues of primary health care are the important considerations, rather than the rarer conditions that are the primary concerns of tertiary centers.

3. The contact with faculty of other universities has provided our faculty the opportunity to exchange epidemiologic, diagnostic, and therapeutic experiences with colleagues in less-sophisticated health care environments and to develop collaborative research projects.

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Safety Hazard With Intravenous Pumps

Sir.—The following patient reports document a safety hazard associated with the IMED (model 960) volumetric infusion pump (IMED Corp, San Diego, Calif).

Patient Reports.—PATIENT 1.—A 3-year-old black girl presented with chronic secretory diarrhea. She had been receiving total parental nutrition since the first year of life. During recent hospitalization for suspected central line sepsis, the patient played with the settings on the IMED volumetric infusion pump (model 960), changing the rate to 632 mL/h, thereby self-administering a 120-mL bolus of the 25% dextrose, with 2.5 g of protein per deciliter of the total parenteral nutrition solution. The patient was discovered in an obtunded state, with blood pressure elevated to 146/94 mm/Hg. Findings of an initial laboratory examination were consistent with a hyperosmolar, hyperglycemic, nonketotic state: glucose, 65.5 mmol/L; serum osmolality, 375 mOsm/L; calcium, 2.74 mmol/L; magnesium, 1.15 mmol/L; phosphorus, 2.29 mmol/L; potassium, 5.7 mmol/L; and serum carbon dioxide, 18 mmol/L. Fortunately, the patient completely recovered 1 hour after this incident. Repeated serum chemistry results obtained 4 hours later were normal.

PATIENT 2.—A 2-year-old black boy was admitted for status asthmaticus. He was being treated with an aminophylline dihydrate drip of 1 mg/kg per hour. A level obtained with this dosage was therapeutic at 17.6 mg/L. Subsequently, the patient played with the controls on the IMED volumetric infusion pump (model 960), changing the rate to provide a 300-mg bolus of aminophylline for 40 minutes. The subsequent theophylline level was 46.1 mg/L. Vital signs were remarkable for tachycardia to 169 beats per minute, and the patient was noted to be agitated. Intermittent gastrointestinal charcoal lavage was initiated. He recovered fully without sequelae.

Comment.—We reported these incidents to the IMED Corp. They concluded that the IMED 960 device could not be adapted to protect the control dials from the hands of inquisitive toddlers and noted that model 980 is equipped with a protective mechanism. Clearly, model 960 is not "childproof." We hope this report will alert other health care professionals to this danger.

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Adhesive Tape Remover Pads: A Risk to the Newborn?

To the Editor.—1,1,1-Trichloroethane (TCE), also known as methyl chloroform, is a solvent used to remove grease, oil, or wax from metal surfaces. Disposable gauze pads saturated with TCE have found wide acceptance in hospitals as an adhesive tape remover. In the newborn intensive care unit, these pads are used to remove tape from intravenous sites and from around the nose and mouth when nasal cannulae and endotracheal tubes are removed. 1,1,1-Trichloroethane is rapidly absorbed through the lungs, and its clinical effects are related to its concentration in the air.^{1,2} 1,1,1-Trichloroethane levels of 160 ppm have been measured in incubator air following the use of adhesive tape remover pads on an infant mannequin.³ The situation exists, therefore, where appreciable quantities might be inhaled by very small infants. This possibility is enhanced if TCE is applied close to the nares. Furthermore, although TCE absorption through the skin has been described as minimal,⁴ newborn skin is relatively permeable, and percutaneous absorption of a va-

riety of agents is known to be enhanced in the newborn.⁵ Increasingly, we are recognizing that topically applied agents that are nontoxic to adults may be absorbed through the skin in amounts sufficient to produce toxic effects in the newborn infant.⁶

1,1,1-Trichloroethane toxic effects in animals and adults includes depression of the central nervous system and, less commonly, hepatic and renal damage. Sudden cardiac death has been described in relation to short-term exposure,⁷ possibly as a result of TCE sensitizing the myocardium to circulating catecholamines⁸ or decreasing myocardial oxygen uptake.⁹

To our knowledge, systemic absorption of TCE among acutely ill low-birth-weight infants has not been studied. The absence of reports of TCE-related harm, however, provides little reassurance about the safety of this agent in sick newborns. Clinicians are most likely unaware of the content of adhesive tape remover pads, and TCE-induced adverse effects in acutely ill newborns could easily be attributed instead to other drugs or the infant's underlying illness.

We have no evidence that adhesive removal pads saturated with TCE (or other halogenated hydrocarbons) are harmful to newborns. However, the potential for systemic absorption and the known risks of TCE should alert clinicians that the use of these pads may be hazardous in sick, low-birth-weight infants.

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Low Serum Complement Levels in Anorexia Nervosa

Sir.—We read the review written by Eichenfield and Johnston,¹ in the May 1989 issue of *AJDC* with great interest, but must disagree with one point, made in Table 1 and in the text. Much of the literature in immunology deals with the abnormalities of anorexia nervosa as if they were the same as the changes seen in malnutrition. Immune abnormalities in the children of Third-World countries, where parasitic infestation abounds and poor hygiene is all too common, are of little relevance to considerations of children of the American middle class, where infection is usually absent. Thus, the two are quite different and should be considered separately.

Several studies of complement levels in individuals with anorexia nervosa have found a decrease in C3,^{2,4} and normal C4.^{2,3,5} Reductions in alternate-pathway components and control proteins^{2,4} have been found as well.

In malnutrition complicated by infection, the most likely cause of hypocomplementemia is a combination of consumption due to ongoing infections and decreased production. The current thinking in anorexia nervosa is that either decreased production of the components³ or a decrease in the complement control proteins C3b inactivator and B1H⁴ is the explanation for the occasional hypocomplementemia found.

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In Reply.—It appears that we do not disagree fundamentally with Drs Sigal and Snyder. Certainly, anorexia nervosa is not the same disease entity as malnutrition in Third-World countries. However, pairing them in the table as complement disorders, due primarily to decreased synthesis, is supported by the experimental evidence that is presently available. As we pointed out, circulating immune complexes and endotoxin in patients with malnutrition could deplete complement, but we believe that the weight of evidence at present favors decreased synthesis as the principal mechanism in both disorders. Although decreased levels of complement control proteins may lead to complement consumption in anorexia nervosa, the primary event is decreased production of these proteins. As we reported, complement abnormalities in both entities are rapidly corrected with appropriate feeding.^{1,2} Perhaps this is the important point.

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On Combination Therapy With Benzoate and Piridoxilate

Sir.—It has been amply demonstrated that administration of sodium benzoate moderates hyperammonemia in

children born with genetic defects in the urea cycle,¹ but the efficacy of benzoate therapy has been questioned on the basis of the limited ability of the body to generate the glycine needed to dispose of waste nitrogen as hippurate.² Accordingly, it was recommended that piridoxilate be administered with benzoate to improve the effectiveness of benzoate therapy. Piridoxilate is a European cardiac drug found to stimulate the conversion of benzoate to hippurate in suspensions of hepatocytes, presumably because piridoxilate metabolism gives rise to glyoxylate and, by transamination, glycine.²

Piridoxilate is unavailable in the United States, so we tested the interaction of the active metabolite, glyoxylate, and benzoate. We found glyoxylate to potentiate benzoate toxicity in vivo and both drugs to inhibit pyruvate carboxylase in vitro, by apparently different mechanisms.^{3,4} The combination inhibited pyruvate carboxylase by 80% at 40 μ mol/L of benzoate (Figure), less than half the mean

blood level during therapeutic use.⁵ Inhibition of pyruvate carboxylase was associated with sharply reduced aspartate levels and depressed synthesis of urea.³ Inhibition of pyruvate carboxylase also blocks gluconeogenesis from lactate.⁶ We report these findings to discourage combination therapy with benzoate and piridoxilate, or any other source of glyoxylate, until the benefit of such therapy has been demonstrated in a suitable animal model.

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The Figure was reprinted with permission from Pergamon Press plc (Cyr DM, Tremblay GC. Potentiation of benzoate toxicity by glyoxylate: inhibition of pyruvate carboxylase and the urea cycle. *Biochem Pharmacol*. In press.).

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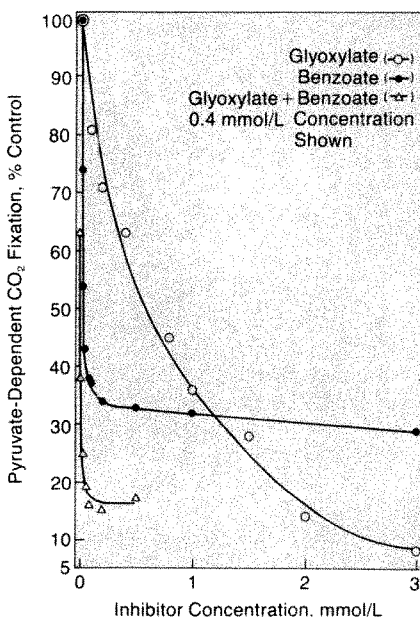
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Inhibition of pyruvate carboxylase by glyoxylate and benzoate. Mitochondria (4 to 6 mg of protein) were incubated at 30°C for 10 minutes in 2-mL reaction mixtures containing carbon 14 potassium bicarbonate (0.3 to 0.5 μ Ci, 20 mmol/L) and benzoate and glyoxylate at the concentrations shown. The reactions were acidified with 0.5 mL of 1.6N hydrochloride at 10 minutes and baked to dryness over a steam bath. Acid-stable radiolabeled product was used as the measure of pyruvate carboxylase activity (from Cyr and Tremblay³).

Jejunal Stenosis: A Delayed Complication of Lap-Type Seat Belt Injury

Sir.—Delayed complications of small-bowel injuries after automobile accidents are difficult to diagnose since the clinical and roentgenographic findings are often inconclusive. We report a late complication, jejunal stenosis. To our knowledge, only one similar case has been reported.¹

Patient Report.—A 15-year-old girl presented with severe abdominal and back pain after an automobile accident several hours earlier. She was a rear-seat passenger and was wearing a lap-type seat belt.

The patient was alert, but a severe drop in her hematocrit value to 0.23, a systolic pressure of 80 mm Hg, and a pulse rate of 120 beats per minute were noted. A large hematoma over the lumbosacral area and a "seat belt" shaped bruise over the lower abdomen were present. There was severe abdominal tenderness to palpation, but the abdomen was not distended, with normal bowel sounds.

The patient received several units of blood and fluid replacement. Following stabilization, computed tomography of the abdomen was performed. A subcapsular splenic hematoma, small amount of free intraperitoneal blood, and a Chance fracture of L3 were discovered. The patient's clinical status improved in the hospital with a regimen of supportive therapy and complete bed rest.

On day 11 of hospitalization, the patient developed severe abdominal pain and vomited brown guaiac-positive fluid. Multiple superficial stress ulcers were seen by endoscopic examination. A repeated computed tomographic scan of the abdomen showed evidence of pancreatitis with no pancreatic pseudocyst or duodenal hematoma. The patient improved following appropriate ulcer therapy.

Nine days later, an increase in bile-stained nasogastric drainage was noted. Repeated abdominal roentgenograms revealed a dilated loop of bowel in the epigastric area interpreted as ileus secondary to pancreatitis and less likely related to early small-bowel obstruction (Fig 1). An upper gastrointestinal tract series was performed the next day and showed complete obstruction at the proximal jejunum. At the obstruction, a smooth, symmetrically narrowed segment of jejunum was seen, characteristic of extrinsic compression (Fig 2).

On exploratory laparotomy, two stenotic segments of jejunum were found, and the corresponding mesentery was fibrotic and devascularized. The proximal segment was matted with other loops of bowel in the right lower quadrant. Resection of the stenotic segments with end-to-end anastomosis and appendectomy were performed. The microscopic examination of the stenotic segments of jejunum revealed fibrosis of the bowel wall and mesentery, consistent with bowel infarction. No definite thrombi were seen within the vessels and there was no evidence of vasculitis. The patient had an uneventful recovery and was discharged 12 days after the surgery with a body cast.

Comment.—Lap-type seat belts are less protective than the three-point combined lap and shoulder belt restraint. With the lap-type belt, injuries occur in the abdomen, pelvis, and lumbar spine.² Although solid viscera are more prone to be injured in blunt abdominal trauma, 5% to 10% of such injuries involve the small bowel and mesentery.³ The small bowel and mes-

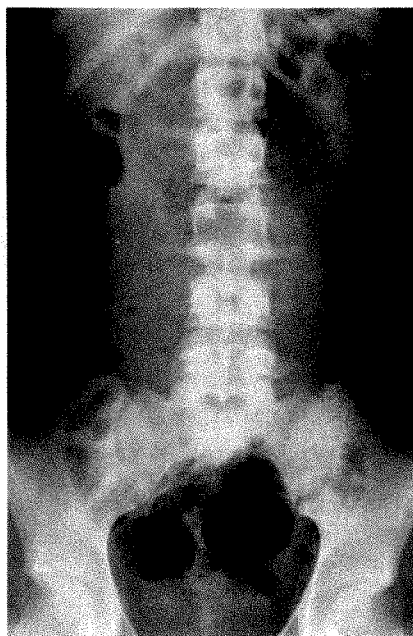


Fig 1.—Plain abdominal roentgenogram demonstrating a dilated loop of small bowel in the epigastrium. Chance fracture of L3 is seen.



Fig 2.—Roentgenogram from upper gastrointestinal tract series showing the markedly dilated proximal jejunum that becomes tubular symmetrically narrowed at the side of obstruction.

entery are more vulnerable to injury because of the anterior midline location of the small bowel where the impact is the greatest. The mechanism of injury is related to shearing and tearing forces exerted by sudden de-

celeration while the victim's pelvis and hips are fixed to the car seat.⁴ Points of fixation of the mesentery are especially prone to damage, such as the ligament of Treitz, the terminal ileum, adhesions from previous surgery, hernias, and shortened mesentery (often found in Crohn's disease).³⁻⁵

Delayed complications of small-bowel trauma include ischemic bowel, perforation, enterocutaneous or colcutaneous fistulas, and small-bowel stenosis with obstruction.⁶ A considerable ischemic insult to the bowel occurs when mesenteric vessels are torn. Severe devascularization and devitalization causes gangrene with subsequent bowel perforation. In a partially infarcted segment of bowel, there is revascularization and the development of fibrotic changes, resulting in stricture formation and bowel obstruction.^{7,8}

Bowel obstruction as a late complication of blunt abdominal trauma has been described in connection with adhesions and posttraumatic hernias.^{9,10} The diagnosis of bowel and mesenteric injuries might not be suspected in a patient with few clinical symptoms or in those patients treated for severe nonabdominal injuries. An association of lumbar spine fractures with intestinal injuries has been described.¹¹

The "seat belt" sign (contusion and ecchymosis in the abdominal area), when present, should alert the clinician and radiologist to the possibility of intestinal injury. Close surveillance for delayed complications is warranted since mortality and morbidity are primarily related to a delay in diagnosis.

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Perinatal Abnormalities and Subhypothalamic Bright Spot on Magnetic Resonance Imaging in Pituitary Dwarfs

Sir.—The survey results on magnetic resonance imaging (MRI) in patients with idiopathic pituitary dwarfism as reported by Root et al¹ were interesting and warrant further observations. The authors demonstrated that MRI in two patients with pituitary dwarfism without asphyxia at birth (one had panhypopituitarism with intact posterior function, and the other had central hypothyroidism) had a signal of high intensity near the optic tract.^{2,3} A small pituitary gland and an unclear defined pituitary stalk were also observed.⁴

To ascertain that the hypopituitary

state was a result of an insult to the pituitary stalk, we compared the T₁-weighted MRI findings of the hypothalamic-pituitary structure in two groups, a total of 14 patients, of idiopathic pituitary dwarfs. The two groups were the following: those with perinatal abnormalities were group 1 (5 boys and 2 girls) (6 had had asphyxia at birth and 1, dystocia with vacuum extraction); those who had had a normal perinatal period were group 2 (6 boys and 1 girl).

A hypoplastic pituitary gland (<2.5 mm in height) was observed in all patients in group 1. Six of them had MRI scans that revealed high-signal intensity near the optic tract (2.5- to 3.0-mm nodule size at the median eminence), suggesting posterior pituitary ectopia⁵ and a hypoplastic pituitary stalk (<0.6 mm wide). The remaining patient in group 1 showed an intrasellar posterior bright spot⁶ with a hypoplastic stalk and a minimal decrease in the size of the anterior pituitary gland.

In all patients in group 2, however, an intrasellar posterior pituitary bright spot with a normal-sized pituitary gland was observed. No patient with a history of perinatal asphyxia was found to have a normal pituitary gland on their MRI scans.

These data reinforced the report of Root et al that the hypopituitary state is due to an insult to the pituitary stalk. However, our data suggested that "ectopic" posterior pituitary may be common in the idiopathic pituitary dwarfs with perinatal abnormalities, but not in those without abnormalities. We may therefore make the sug-

gestion from these findings that idiopathic pituitary dwarfism can be further classified into two or more subgroups—one due to perinatal asphyxia and the others not.

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Leads From the MMWR

Morbidity and Mortality Report
Centers for Disease Control, Atlanta

Current Trends, Measles—United States, 1988

MMWR. 1989;38:601-605

IN 1988, a provisional total of 3411 measles cases was reported to the Division of Immunization, Center for Prevention Services, CDC, 7% less than the 3652 cases reported during the same period in 1987 (Figure 1).¹ The overall incidence rate for 1988 was 1.4 cases per 100,000 population. Nine states reported greater than or equal to 100 cases and accounted for 2802 (82.1%) cases: California (836), Pennsylvania (542), New Jersey (402), Texas (287), Virginia (239), Florida (170), Colorado (117), Ohio (109), and New Hampshire (100). Seven states had incidence rates greater than 2.0 per 100,000 population: Montana (10.7), New Hampshire (9.2), New Jersey (5.2), Pennsylvania (4.5), Virginia (4.0), Colorado (3.5), and California (3.0). Thirty-six states and 211 (6.7%) of the nation's 3138 counties reported measles cases.

A total of 3176 (93.1%) cases met the standard clinical case definition for measles,* and 1001 (29.3%) were serologically confirmed. The usual seasonal pattern was observed with cases peaking during weeks 18-25 (May and June).

Eighty-seven (2.6%) cases were known to be imported from other countries. An additional 126 (3.7%) cases were epidemiologically linked to imported cases within two generations. Fifty-seven outbreaks (five or more epidemiologically linked cases) were reported and accounted for 89.3% of all cases. Six outbreaks had greater than 100 cases and accounted for 52.7% of all reported cases. Most outbreaks occurred among school-aged children. The largest outbreak (611 cases) occurred in Los Angeles among unvaccinated preschool-aged children.

The incidence rate of measles decreased between 1987 and 1988 for 0-4-, 5-9-, and 10-14-year-olds, and increased in 15-19- and 20-24-year-olds. The highest incidence rate (5.8 per 100,000) occurred in 15-19-year-olds (Table 1).

Complications were reported in 408 (12.0%) cases. Otitis media was reported in 183 (5.4%); diarrhea, in 128 (3.8%); pneumonia, in 93 (2.7%); and encephalitis, in four (0.1%). Three

hundred sixty-eight (10.8%) persons were hospitalized. Three measles-attributable deaths were reported (case-fatality rate: 0.9 deaths per 1000 cases).

Of the 2179 (63.9%) patients for whom setting of transmission was reported, 871 (40.0%) acquired measles in primary or secondary schools; 267 (12.3%), in colleges or universities; 553 (25.4%), at home; 127 (5.8%), in medical settings; 69 (3.2%), in day care; and 292 (13.4%), in a variety of other settings.

A total of 1548 (45.4%) patients had been vaccinated on or after the first birthday (Table 2), including 729 (21.4%) who were vaccinated at 12-14 months of age. One thousand eight hundred sixty-three (54.6%) persons were not vaccinated on or after the first birthday. Of these, vaccination would have been routinely indicated** for 803 (23.5%). Six hundred twenty-eight (18.4%) cases occurred in persons for whom vaccine was not routinely indicated, and 432 (12.7%) were unvaccinated for other reasons.

Of the 3411 reported cases, 1942 occurred among school-aged children. Of these, 1339 (68.9%) had been appropriately vaccinated. Most of the vaccine failures occurred in persons 12-19 years of age (Figure 2).

Reported by: Div of Immunization, Center for Prevention Svcs, CDC (MMWR Vol 38 No. 35).

CDC Editorial Note: Since 1983, the number of reported measles cases increased annually until 1986, then decreased in 1987 and slightly in 1988 (Figure 1). In 1988, the age distribution of cases was similar to those in previous years. As in previous years, primarily two types of outbreaks occurred: those among highly vaccinated (vaccine coverage greater than 90%) school-aged children and those among unvaccinated preschool-aged children.²

The epidemiology of measles points to two major impediments to measles elimination—unvaccinated preschool-aged children, allowing large outbreaks in inner-city areas, and vaccine failures, accounting for outbreaks in highly vaccinated school-aged popula-

tions. Therefore, in January 1989, the Immunization Practices Advisory Committee (ACIP) issued revised recommendations.³ First, ACIP lowered the age for routine measles vaccination in inner-city areas to as low as 9 months so that children would be vaccinated before they could be exposed to measles, and coverage would therefore be increased. Second, ACIP recommended that, for outbreaks in schools, previously vaccinated persons in specific target groups be revaccinated in affected schools and unaffected schools at risk for transmission. The groups targeted for revaccination are persons vaccinated before 1980 or vaccinated at 12-14 months of age. The rationale for choosing the 1980 date has been described.³ Data from four recent outbreak investigations have shown that persons vaccinated before 1980 are at increased risk for measles (Table 3). This is believed to be due primarily to a higher rate of failure of initial seroconversion for persons vaccinated before that time. Although children vaccinated between 12 and 14 months of age are at higher risk than are children vaccinated at older ages, only a minority of children with measles in most outbreaks have been vaccinated between these ages.¹

Implementation of these new outbreak-control recommendations during 1989 has been expensive because of the large number of outbreaks and cases. In the first 26 weeks of 1989, 8553 cases were reported, a 392% increase over the same period in 1988. More than 90 outbreaks have been reported; most have occurred in secondary schools and colleges. Seventy-one colleges have reported at least one case of measles. The largest outbreak has occurred in Houston, with greater than 1700 cases, primarily among unvaccinated preschool-aged children. Several states have spent several hundred thousand dollars each to revaccinate young adults in secondary schools and colleges.

Because of continued outbreaks among school-aged children, in May 1989, the ACIP decided to recommend a routine two-dose measles vaccination schedule. The second dose will be administered at entry to kindergarten

or first grade (children 4-6 years of age). A two-dose schedule will decrease primary vaccine failures and thus the number of susceptibles and measles outbreaks in school-aged children. In addition, outbreak-control measures will be simplified. Detailed recommendations for this schedule and outbreak control are being formulated and will be published in the fall of 1989. Until then, the previously published schedules and recommendations should be followed. The American Academy of Pediatrics has also developed a routine two-dose measles vaccination schedule, which recommends that the second dose be given at entry to middle or junior high school.⁷

The two-dose schedule will not affect outbreaks in inner-city areas among unvaccinated preschool-aged

children. Prevention of such outbreaks requires intensive efforts directed at increasing age-appropriate immunization levels, which are being initiated by CDC and state and local health departments. These include activities in service delivery, assessment, information/education, operational research and surveillance. The two-dose schedule and intensive efforts to raise age-appropriate immunization levels should facilitate the goal of measles elimination in the United States.

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*Fever greater than or equal to 101 F (greater than or equal to 38.3 C), if measured; generalized rash lasting greater than or equal to 3 days; and at least one of the following: cough, coryza, or conjunctivitis.

**Cases in persons who were eligible for vaccination but who were not vaccinated.

Aquarium-Associated *Plesiomonas shigelloides* Infection—Missouri

MMWR. 1989;38:617-619

IN JULY 1988, a community hospital in southeastern Missouri reported isolating *Plesiomonas shigelloides* from the stool of a 14-month-old girl with watery diarrhea (no blood or mucus) and fever. Her highest recorded rectal temperature was 102 F (38.9 C). Her stool was negative for *Campylobacter*, *Salmonella*, *Shigella*, *Yersinia*, *Aeromonas*, and rotavirus. The child was treated with trimethoprim/sulfamethoxazole, and her illness resolved after 5 days.

The child had consumed no shellfish and had never traveled more than 80 miles from her home. She had consumed water only from the municipal system and recently had waded in two area lakes. She attended a day-care center, but no other children in her age group were reported ill. The child did not have an aquarium or other close association with animals. However, 1 evening each week, the child stayed in the home of a babysitter who kept piranhas in an aquarium. When the aquarium was cleaned, the water was poured into the bathtub. The child routinely was bathed in the bathtub before going home. The babysitter reported that the child could have been bathed immediately after the aquarium water had been poured into the bathtub.

P. shigelloides was isolated from samples of aquarium water submitted

to the State Public Health Laboratory. However, plasmid studies were not performed, and it was not determined whether the bacterial strain isolated from the child's stool was identical to that isolated from the babysitter's aquarium.

To estimate the prevalence of *P. shigelloides* in tropical fish tanks, investigators from the Missouri Department of Health (MDH) surveyed aquarium water samples from several sites in Missouri (Table 1). Samples were taken from 18 aquariums, including at least two tanks from each of Missouri's six regional health districts. *P. shigelloides* was isolated from four (22%) of the 18 tanks. The four tanks were located in three different pet shops: two in central Missouri and one in eastern Missouri. Employees of the three pet shops reported no health problems in the fish in the culture-positive tanks.

MDH advised managers of all surveyed pet shops to have employees wash hands after contact with aquarium water or fish. No special precautions were recommended to managers of shops from which *P. shigelloides* was isolated. In addition, the babysitter was advised to clean the tub thoroughly using chlorine bleach after discarding the aquarium water and before using the tub for bathing.

Reported by: PS Tippen, A Meyer, EC Blank,

DrPH, State Public Health Laboratory, HD Donnell, Jr, MD, State Epidemiologist, Missouri Dept of Health. Div of Field Svcs, Epidemiology Program Office, CDC. (*MMWR* vol 38, No. 365)

CDC Editorial Note: *P. shigelloides*, a gram-negative bacterial rod, is an opportunistic pathogen in the immunocompromised host and has been suspected to cause diarrheal illness in normal hosts.^{1,2} However, the organism failed to produce illness in volunteer feeding studies, and its role as an enteric pathogen remains unproven.¹ Persons with *P. shigelloides* infection typically describe a self-limited diarrhea, sometimes with blood and mucus in the stool; appropriate antibiotic therapy appears to shorten the duration of illness.^{3,4} *P. shigelloides* can also cause cellulitis and septicemia.

This organism has been isolated from surface water, the gut of freshwater fish, and many animals (including dogs and cats) and is particularly common in tropical and subtropical habitats.⁵ In humans, most isolates have been from stools of patients with diarrhea who live in tropical and subtropical regions of Asia, Africa, and Australia; isolations from Europe and the United States have been rare and usually associated with foreign travel or consumption of raw oysters.^{3,6}

Although no other *P. shigelloides* gastrointestinal infections associated with aquarium water have been re-

ported, the frequency of *P. shigelloides* in pet shop aquariums reported here suggests this could be a source of this rarely recognized infection. Basic precautions, such as handwashing after contact with aquarium water and preventing the contamination of potable or bathing water by aquarium water, should decrease transmission of potentially pathogenic microorganisms from aquarium water.

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Publication of Guide for Developing Policies for HIV-Infected Students and School Staff

MMWR. 1989;38:614-615

THE NATIONAL ASSOCIATION of State Boards of Education (NASBE) is one of 20 national organizations that receive assistance from CDC to help schools provide effective health education programs to prevent the spread of human immunodeficiency virus (HIV). NASBE has published a guide that CDC commends to its readers: *Someone at School Has AIDS: A Guide to Developing Policies for Students and School Staff Members Who Are Infected with HIV*.

To develop the guide, NASBE convened experts in medicine, public health, education, and law* and has

recommended scientifically and legally based policy statements that local and state departments of education can use in developing policies for HIV-infected students and staff. The guide addresses infection control, HIV-infected students and school staff, confidentiality, and HIV-antibody testing. The guide also includes resources for further information about HIV education, discrimination, disease reporting, policymaking, and crisis management.

Copies of the guide are available from NASBE, Publications Department, 1012 Cameron Street, Alexandria, VA 22314; telephone (703) 684-4000.

*Representatives of the following organizations participated in developing and/or reviewing the guide: American Academy of Pediatrics, American Association of School Administrators, American Bar Association, American Federation of Teachers, American Medical Association, Association of State and Territorial Health Officials, CDC, Council for Exceptional Children, Council of Chief State School Officers, Intergovernmental Health Policy Project, Michigan Department of Education, National Association of Elementary School Principals, National Association of School Nurses, National Association of Secondary School Principals, National Congress of Parents and Teachers, National Education Association, National School Boards Association, U.S. Department of Education, and U.S. Department of Justice.

Enterovirus Surveillance—United States, 1989

(*MMWR* 1989;38:563)

NONPOLIO ENTEROVIRUS (NPEV) surveillance data show that isolates from March through May predict the types likely to be isolated in July through December, which includes the peak enterovirus season.¹ State virology laboratories have reported to CDC 31 NPEV isolates obtained from patients in the United States from March through May 1989. Coxsackievirus B5 was isolated most frequently (16 isolates), followed by echovirus 6 (two isolates), and coxsackievirus B3, coxsackievirus A3, and echovirus 9 (one each); 10 isolates were reported as untyped enteroviruses.

Of the 946 NPEV isolates reported in 1988, the six most common were echovirus 11 (18.6%), echovirus 9 (14.1%), coxsackievirus B4 (10.6%), coxsackievirus B2 (9.2%), echovirus 6 (6.2%), and coxsackievirus B5 (5.1%). In 1988, these six NPEV types rep-

resented 64% of the total enterovirus isolates.

Reported by: State virology laboratory directors. Respiratory and Enterovirus Br, Div of Viral and Rickettsial Diseases, Center for Infectious Diseases, CDC. (*MMWR* vol. 38, no. 32)

CDC Editorial Note: Enteroviruses are a group of 65 different common agents that cause 10-20 million mild upper respiratory infections in the United States every year. Enteroviruses are also responsible for tens of thousands of hospitalizations for aseptic meningitis each year. Knowledge of the common enterovirus subtypes may assist diagnostic laboratories in more rapidly identifying enterovirus isolates and assist public health officials in recognizing outbreaks of enteroviral disease.

Since 1970, state health department laboratories have reported on enterovirus serotypes to CDC approximately 6-8 weeks after specimens are submit-

ted for identification. From 1970 through 1983, the six most common isolates in March through May accounted for an average of 59% of the isolates in July through December, and for this period in 1984-1988, for 50%-58% of the isolates.

The NPEV isolates reported in early 1989 included many coxsackievirus B5 and several of three other types; however, the limited number of these four types makes it impossible to predict at this time that they will be common isolates in 1989. The top six isolates reported in 1988 and each of the four isolates reported in March through May 1989 were in the 15 most frequent isolates for 1970-1983.¹

Reference

1. Strikas RA, Anderson LJ, Parker RA. Temporal and geographic patterns of isolates of non-polio enterovirus in the United States, 1970-1983. *J Infect Dis* 1986;153:346-51.

NEW FROM McNEIL

**Pedia
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A new therapeutic alternative for fever

Antipyretic efficacy

In children with temperatures greater than 102.5°F, ibuprofen 10 mg/kg is more effective than ibuprofen 5 mg/kg or acetaminophen 10 mg/kg.¹

PediaProfen is indicated for the reduction of fever in children 6 months and older.

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See brief summary of Prescribing Information. Significant adverse effects are reported with NSAIDs. Serious as well as minor side effects can occur with long-term use of high-dose ibuprofen. In clinical studies with over 400 pediatric patients, no significant adverse reactions were reported during short-term therapy for fever.²

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Designed for compliance; well liked by patients in clinical studies.²

References:

1. Walson PD, et al. Ibuprofen, acetaminophen and placebo treatment of febrile children. *Clin Pharmacol Ther.* 1989;46:9-17. 2. Data on file, McNeil Consumer Products Company.

From the children's fever relief specialist

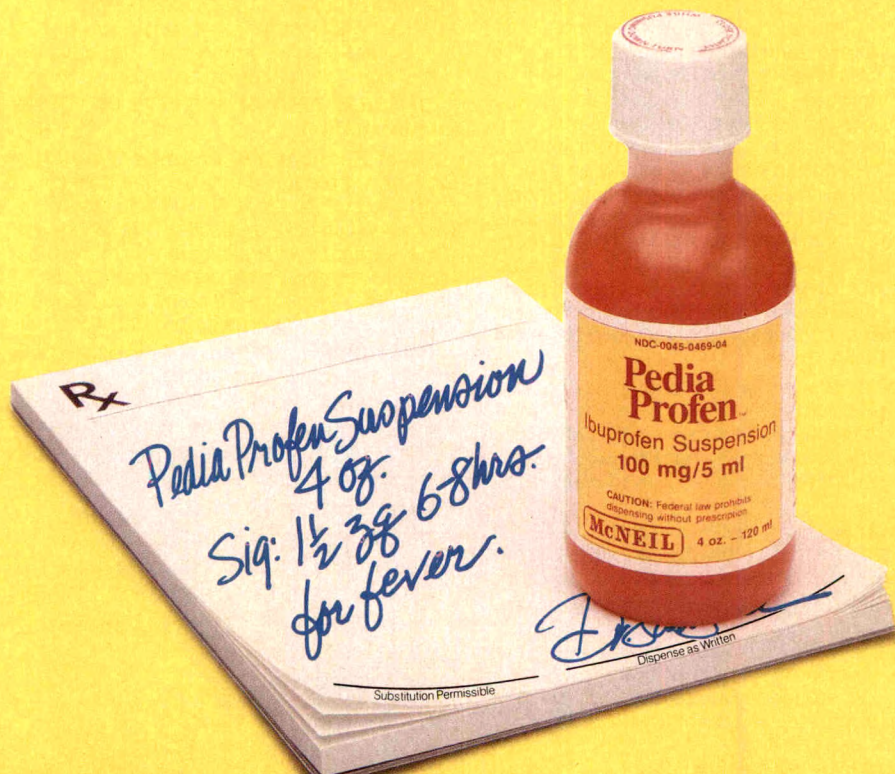
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The following is a brief summary only. Before prescribing, see complete prescribing information in **PediaProfen** labeling.

INDICATIONS AND USAGE: **PediaProfen** is indicated for the reduction of fever in patients aged 6 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CLINICAL PHARMACOLOGY: Controlled clinical trials comparing doses of 5 and 10 mg/kg ibuprofen and 10-15 mg/kg of acetaminophen have been conducted in children 6 months to 12 years of age with fever primarily due to viral illnesses. In these studies there were no differences between treatments in fever reduction for the first hour and maximum fever reduction occurred between 2 and 4 hours. Response after 1 hour was dependent on both the level of temperature elevation as well as the treatment. In children with baseline temperatures at or below 102.5°F both ibuprofen doses and acetaminophen were equally effective in their maximum effect. In those children with temperatures above 102.5°F, the ibuprofen 10 mg/kg dose was more effective. By 6 hours children treated with ibuprofen 5 mg/kg tended to have recurrence of fever, whereas children treated with ibuprofen 10 mg/kg still had significant fever reduction at 8 hours. In control groups treated with 10 mg/kg acetaminophen, fever reduction resembled that seen in children treated with 5 mg/kg of ibuprofen, with the exception that temperature elevation tended to return 1-2 hours earlier.

CONTRAINDICATIONS: **PediaProfen** should not be used in patients who have previously exhibited hypersensitivity to ibuprofen, or in individuals with all or part of the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy. Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving **PediaProfen**, the drug should be discontinued and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with ibuprofen, therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

PediaProfen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation, but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range), in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying

hemostatic defects, **PediaProfen** should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients on **PediaProfen** should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

In order to avoid exacerbation of disease of adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of **PediaProfen** may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Safety and efficacy of **PediaProfen** in children below the age of 6 months has not been established.

Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of **PediaProfen** is not recommended during pregnancy.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Adverse reactions occurring in 3% to 9% of patients treated with ibuprofen: nausea, epigastric pain, heartburn, dizziness, rash. *Adverse reactions occurring in 1% to 3% of patients:* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract, headache, nervousness, pruritus, tinnitus, decreased appetite, edema, fluid retention (generally responds promptly to drug discontinuation). Still other reactions (less than 1 in 100) have been reported, and are detailed in the full summary of prescribing information.

DOSAGE AND ADMINISTRATION: Shake well prior to administration.

Fever Reduction in Children 6 months to 12 years of age:

Dosage should be adjusted on the basis of the initial temperature level (See CLINICAL PHARMACOLOGY for a description of the controlled clinical trial results). The recommended dose is 5 mg/kg if the baseline temperature is less than 102.5°F or 10 mg/kg if the baseline temperature is greater than 102.5°F. The duration of fever reduction is generally 6-8 hours and is longer with the higher dose. The recommended maximum daily dose is 40 mg/kg.

Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for the relief of pain in adults.

In controlled analgesic clinical trials, doses of ibuprofen greater than 400 mg were no more effective than 400 mg dose.

HOW SUPPLIED: **PediaProfen** Ibuprofen Suspension 100 mg/5 ml (teaspoon)—

orange, berry-vanilla flavored

Bottles of 4 oz (120 ml)..... NDC 0045-0469-04
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Being Just a Husband Is No Fun

E. Richard Stiehm, MD

One of our stalwarts on the Editorial Board has had a unique experience in the last few years; he has been a transcontinental spouse. In one of his two lives, as he so aptly describes, he has learned how the "other half" feels to be "the spouse of . . .". His article has currency, not only for the experience itself and its reflection of some marriages today, but because such experience will become commonplace in the future. More and more women have entered medicine and other professional careers and are achieving hierarchical status within their chosen fields. Their male spouses will now have to cope, as our female spouses have for decades, with a quite different role than that of the stereotypic dominant male, so prominent in American conception.

My wife, Shirley, and I attended a retreat for first-year freshman medical students not too many years ago. I was privileged to be a member of the small break-out group that consisted of spouses and so-called significant others of the medical students. To my amazement and education, the majority were male (correspondingly, most of the students attending the retreat were female), and the attitudes displayed echoed what I had heard female spouses of the faculty saying for years. For example, one male businessman said, "Do you mean that if she wants to take a residency in Seattle, I'd have to give up my business and follow her? . . . Hell, no!" Perhaps he would be like Dr Stiehm and conduct a Los Angeles-Tucson-to-Seattle marriage. Another complained, "At every party we go to, all they talk about is medicine! Don't they have any other interests?" And on through the day.

On reflection, Shirley and I realized that medical marriages are in for some surprises in the future. Dr Stiehm's experience is just the forerunner of many like it in the future. We will have to find new ways to make relationships work and to be sustained over the years. Men will have to learn to be secondary in interest to friends and colleagues of their successful female spouses. Men will have to learn to tolerate highly technical cocktail-party and dinner-party talk outside their sphere of knowledge, and interest, and scope.

We are truly in for a brave new tomorrow. Dr Stiehm's firsthand description will be recognized by many today as pertinent and will be a blueprint for the future. May all have the wisdom and humor of Judy and Dick Stiehm!—ED

In Los Angeles, Calif, I am taken seriously. In Miami, Fla, I am not. The contrast is illuminating and humorous, but not entirely pleasant.

At home in Los Angeles, my identity is as a physician and teacher. I take care of kids with acquired immunodeficiency syndrome, teach pediatrics at UCLA Medical School, write papers, give lectures, and direct a research laboratory. Others regard me, I hope, as a useful, contributing member of society.

My main problem is that a year ago, my wife Judy, a political science professor, became provost of a large state university in Miami. So we have the proverbial bicoastal marriage, and I try to get to Miami twice a month.

Don't get me wrong, I'm not jealous or anything. I'm proud of her and know how hard she has worked through many moves, three children, and the barriers working women of her generation had to face.

My life changes drastically in Miami. I become a nonperson, without a work identity. Socially, however, I can't complain. We attend concerts and plays, parties and receptions, lectures and sports events. But sometimes I can't help feeling like Prince Philip—the charming consort, who lives in his wife's reflected glory.

This life is like a spicy Chinese egg roll: tasty at first, often hard to digest, but definitely not suitable for a daily menu. Let me describe a weekend last December, for example.

Judy wanted me to come that weekend because she was giving a Christmas party that would include her colleagues and friends in the Miami establishment. She met me at the airport Friday afternoon and was frantic because my flight was over an hour late, as usual. She looked relieved that I hadn't checked any luggage.

I drove, with her directions, to the Merrick House in Coral Gables, Fla, an historic home that would easily accommodate the 200 guests. She needed to use the time to check the guest list. Her secretary had carefully prepared cards

on each guest, with the spouse's first name on them.

Judy instructed me on whom I should be sure to talk with, and who was who in the university and the community. I told her it was an exercise in futility because I would forget their names as soon as she told them to me. She said that was OK, it was a good review for her.

When we arrived, there wasn't much for me to do, since the student caterers had things well under control, and Judy ("Dr Stiehm") was involved in giving them last-minute instructions.

So I picked up the *Miami Herald* and noticed that her boss, the university president, was quoted as describing his job as "like juggling five balls, while on roller skates, perched on top of a flag pole." I pointed this out to Judy, who immediately dispatched me to buy balls, skates, and a small flag pole for a gag gift to give her boss at the party. At last I felt useful.

The party was a grand success. People told me what a good job "Judith" was doing and asked me, "By the way, what do you do in Miami?" I had to confess,

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From the Department of Pediatrics, UCLA.
Reprint request to Department of Pediatrics,
UCLA, 10833 Le Conte Ave, Los Angeles, CA
90024-1752 (Dr Stiehm)

"Nothing, just visiting my wife." Then they asked me when I was moving there, away from the smog and crime of Los Angeles. Several asked if we played mixed doubles.

The next day, Judy's old friend, Betty Friedan, came to town to give a talk. Betty wanted to see Judy's office, so we went there first, with me tagging along, listening to them discuss where the women's movement is now and whether the press would cover the lecture. When we got there, Betty and I admired the paintings, the teak desks, the thick carpets, and the balcony. At least Judy's 12-hour days were conducted in civilized surroundings.

Then it was time for Betty's speech. There was a good crowd, about 190 women and 10 men. "It's an overflow," said Judy as we arrived. She was going to introduce Betty, so they went up front, while I took a seat in the back.

Betty covered what couples can do to cope with two-career marriages in the 1980s. One inevitable result, she said, was the birth of the commuter marriage. I consoled myself that we were on the cutting edge of a trend, even in our 50s.

Afterward there were punch and

cookies for everybody. Betty and Judy were the two stars of the show, the ones that people surrounded. I got a drink and looked around for someone to talk with. Almost by a tribal instinct, I started talking with the only other man at the reception. He was a dour associate professor who criticized the speech, the acoustics, even the cookies. He wanted to know why I came to the lecture. After I told him that my wife was the provost, he suddenly became very interested in me, especially in telling me what needed to be done about the university's problems—higher faculty salaries, bigger offices, a lighter teaching load, better parking, things like that. He hinted I should pass these insights on to my wife.

Once he wandered off, I found myself alone. I had the feeling that people were looking through me or over my shoulder. Finally, two nice older ladies came over to say hello to me. I had become an expert at small talk by then, and we had a pleasant conversation. I found out that they were co-owners of a pet boardinghouse. (Neither was named Muriel.) They knew who my wife was and commented on how "pretty" she was. Then came the familiar question: "When will

you be moving to Miami?"

Whenever I say it—that I have no plans to move to Miami—the reaction is pretty much the same: surprise and disappointment, with a little disapproval thrown in. These ladies were no different and quickly changed the subject.

"Does your wife own a pet?" one of the women asked. The other added, "She must travel a lot. Doesn't she need a place to keep her pet?" I couldn't help wondering if that was the only reason they were talking with me. I said, "No, I'm sorry. She doesn't have a pet." But to cushion the blow, I added that if she did get one, I would tell her about their boardinghouse. Then I introduced them to Judy and Betty. They were so pleased that afterward they thanked me for the introduction.

So went the weekend in Miami. Others have been more or less like that one. Now I know how many wives feel at their husbands' business dinners or medical conventions.

It's a little hard on my male ego being just a husband. Maybe that's why I haven't moved to Miami. All in all, it's better to be the big wheel than the big wheel's spouse.

Age-Related Patterns of Violent Death, Cook County, Illinois, 1977 Through 1982

Katherine K. Christoffel, MD, MPH; Nora K. Anzinger, RN; David A. Merrill

• To clarify age-related patterns of violent death in childhood, a study was undertaken of medical examiner records concerning 437 deaths of Cook County, Illinois residents, aged younger than 15 years, who died from 1977 through 1982, and whose deaths were ruled as homicides or of an undetermined manner. Males outnumbered females after the age of 1 year. Black children were overrepresented. Perpetrators were usually parents for victims aged younger than 5 years and others for victims aged 5 years or older. Different circumstances of death characterized victims who were younger (mainly beatings) and older (mainly gunshots). Incidence was associated with urban residence and poverty, and it was highest among the youngest and oldest children. Striking differences were found in death rates for age subgroups within standard age groupings (eg, 19.77/100 000 for 1 and 2 years and 6.35/100 000 for 3 and 4 years). Different geographic areas had the highest rates for younger and older victims. We conclude: (1) Separate strategies are needed to protect the two groups at highest risk for homicide: black children aged younger than 3 years and older than 11 years in poor urban areas. (2) Standard homicide reporting practices should include narrow age groupings. (3) Age-related patterns of child homicide must be considered in the planning of prevention trials. (4) Research is needed to clarify why children of different ages are at different risks in different communities.

(AJDC. 1989;143:1403-1409)

Accepted for publication May 22, 1989.

From the Division of General and Emergency Pediatrics, Department of Pediatrics, Northwestern University School of Medicine, Children's Memorial Hospital, Chicago, Ill (Dr Christoffel), and the Chicago Area Geographic Information Study, Department of Geography, University of Illinois, Chicago (Mr Merrill).

Presented in part at the annual meeting of the Ambulatory Pediatric Association, Anaheim, Calif, April 30, 1987, and at the First National Symposium on Child Abuse Fatalities, Chicago, Ill, July 14, 1987.

Reprint requests to Division of General and Emergency Pediatrics, Department of Pediatrics, Northwestern University School of Medicine, Children's Memorial Hospital, 2300 Children's Plaza, Box 46, Chicago, IL 60614 (Dr Christoffel).

Violence, including assault and child abuse and neglect, has become one of the leading causes of death in childhood and adolescence.^{1,2} Preventive approaches will grow from the understanding of the epidemiologic features of homicides. Published reports have provided information on varying numbers of victims, in various time periods, age ranges, and settings.³⁻¹⁹ Cook County, Illinois, has an incidence of violent child death that is sufficiently high so that several recent years have provided an adequate number of deaths to describe clearly contemporary patterns. The county includes urban, suburban, and rural areas, and it has had its Office of the Medical Examiner, (Chicago, Ill) staffed by forensic pathologists since 1977. A 6-year retrospective study of violent child deaths was undertaken in Cook County to clarify which features from other locales and eras should guide prevention efforts in the 1990s and beyond.

MATERIALS AND METHODS

Deaths handled by medical examiners and coroners are assigned one of five "manners of death": homicide, suicide, accident, natural, or undetermined. Cases that are ruled of an undetermined manner include those in which information is lacking to prove intentional injury or neglect, but in which there is evidence that precludes assigning the death a natural or accidental manner. The records of the Office of the Cook County Medical Examiner were reviewed to identify deaths of resident children, aged younger than 15 years, that were recorded from 1977 through 1982 with assigned manners of homicide or undetermined. Both manner of death categories were included to avoid an underestimation of the true incidence of violent death.

Twenty-six eligible records (5%) were not obtainable. Twelve cases were excluded from the analysis because of out-of-county residence. Twenty-five undetermined cases were excluded because available information indicated that they were almost certainly not violent deaths: 3 were medical/surgical mishaps, 4 were probable or suspected suicides,

5 were deaths that were most likely related to an underlying disease or condition, 2 were cases of sudden infant death syndrome, 4 were probable cases of sudden infant death syndrome, 3 were cases of probable aspiration, 1 was most likely to have been an unintentional injury, and 3 were fetal deaths before 6 months' gestation. This left 437 cases for analysis.

Uniform data were abstracted by one of the investigators (N.K.A.). Information was abstracted on demography, anatomy, and death circumstances; the information that related to death circumstances was based on available reports by police, medical examiner, and/or protective service investigators.

If a birth date was missing in the record, the best estimate of the year of age was entered based on the age listed on the death certificate. Latin and Oriental decedents were identified whenever possible, but familiarity with the records suggests that some of these may, at times, have been recorded as white. Data quality was assessed on a sample of study cases. For each case, 10 data items were reviewed. The overall transcription accuracy was 98%.

A census tract was assigned to each case based on the decedent's recorded address. As fewer than 3% of all records reviewed concerned noncounty residents, victims without recorded addresses (or with addresses not assignable to a census tract) were included in the analyses that did not require census data.

Data were analyzed (by D.A.M.) using the SAS computer program: frequency, χ^2 test, means, Scheffé test (to reduce the likelihood of a spurious identification of intergroup differences when a large number of comparisons was made), correlation, analysis of variance (general linear model for unbalanced data), and multiple linear regression.²⁰ Findings were considered to be significant for $P < .05$. Incidence rates were calculated as mean annual rates per 100 000 population in the 1980 census. For mapping and some analyses, area rates were calculated for community areas (standard groupings of census tracts) as the overall rate in incidence census tracts. This approach was used to avoid artificially high rates due to a high incidence in some individual tracts if only separate tracts were used for the analysis, and artificially low rates if the population in nonincidence

tracts were used to calculate area rates. For the analysis of social/demographic correlates of age-specific rates, multiple linear regression analysis was used, with incidence rates for victims aged younger than 1 year and aged 10 through 14 years dependent, and independent variables entered in a stepwise fashion ($P \leq .15$ for entry into and retention in the model). The census tract descriptor variables that were entered into the analyses were as follows: infant/toddler (age <3 years) population; teen (ages 10 through 19 years) population; child (ages 0 through 19 years) population; percentage of female-headed households; crowding (percentage in units with >1.01 persons per room); family median income; percentage of population nonwhite; homicide rate for 10- to 14-year-old children for the less than 1-year-old model; and homicide rate for the children aged younger than 1 year for the 10- to 14-year-old model.

Definitions

Tables in this report use terms that require definition. *Violent deaths* included both cases ruled as a homicide and those ruled as of an undetermined manner. As described above, the data excluded the undetermined deaths that were most likely to be due to causes other than assault, child abuse, or child neglect.

Based on the records reviewed, cases were assigned to one of nine *injury circumstances*: (1) blunt injury included trauma to the head and other body parts due to beatings, (2) gunshot, (3) arson (resulting in smoke inhalation), (4) fall, (5) burn, (6) neglect, (7) malnutrition, (8) strangulation and stabbing (excluding dismemberment), or (9) other. Head trauma was not separated from other types of beatings as originally intended, because most cases involved injuries both to the head and other body parts. Strangulations and stabbings were grouped together because of common situations: psychotic perpetrators, intruders, and desolate locales.

Perpetrators and Situations

Perpetrators were categorized as mother only, any father (father or stepfather only; mother and father or stepfather), other (acquaintance, including mother's boyfriend; stranger; unspecified), or unknown.

Fatal *injury situations*, the detailed sequence of events leading to death, were reconstructed when feasible from available information. These were grouped into clinically meaningful categories for tabulation and discussion. These categories often were not comparable (eg, argument and deserted site) due to variably available information.

Further details on the methods that we used can be obtained from the report on this

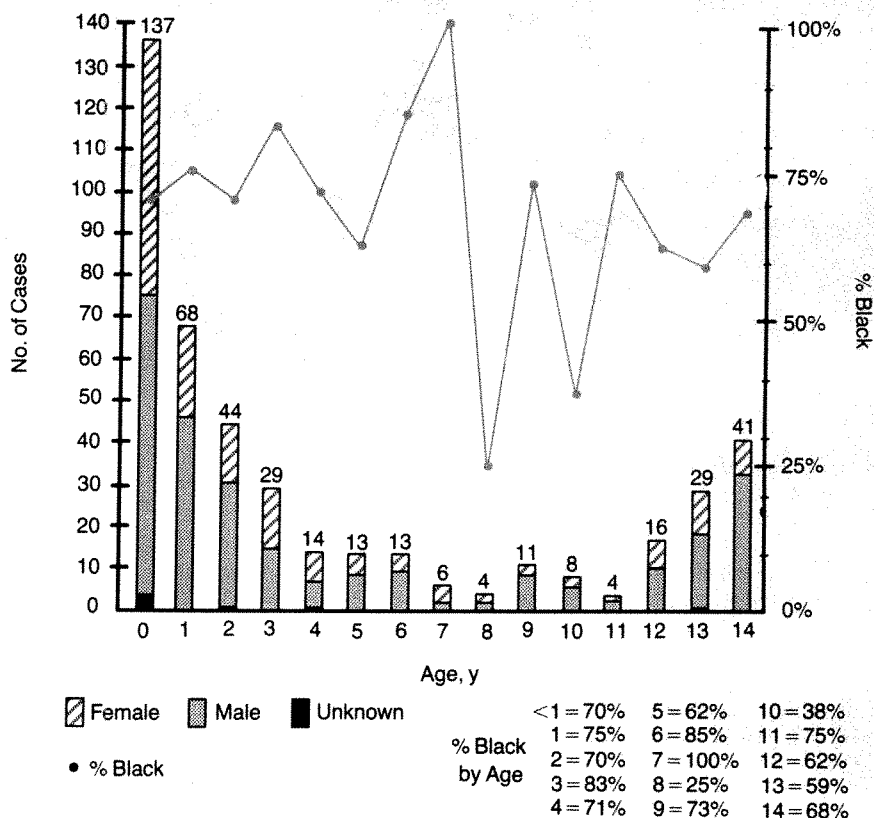


Fig 1.—Violent deaths of children in Cook County, Illinois, from 1977 through 1982. Study cases by age, gender, and race. Age in years indicates youngest age in category (eg, 0 is <12 months, 1 is 12 through 23 months, etc.).

study to the US Department of Health and Human Services, Washington, DC.²¹

RESULTS Overview of Cases

The study included 437 cases: 230 homicides, 206 of undetermined manner and 1 unclassified. The annual number of cases ranged from 59 (1977) to 88 (1980). There were more victims aged younger than 5 years than victims aged 5 years or older in winter (January, November, and December, 33% vs 16.5%) and more victims aged 5 years or older than victims aged younger than 5 years in summer (June, July, and August, 36.5% vs 16%, $P < .01$).

Sixty-one percent of victims were male, with males substantially outnumbering females after the age of 1 year. Approximately one third of victims were younger than 1 year, and almost half were younger than 2 years. The age distribution was U shaped. Black children were overrepresented: 70% of cases vs 34% of children younger than 15 years in Cook County in 1980 (D.

Injury Circumstance	No. (%)
Blunt injury	147 (34)
Gunshot	72 (16.5)
Arson	46 (10.5)
Hit-and-run	17 (4)
Strangulation/stabbing	29 (7)
Fall	8 (2)
Burn	8 (2)
Neglect/malnutrition	6 (1)
Other/unknown	93 (22)
None recorded	11 (2.5)
Total	437 (100)

McGrier, US Census Bureau, Chicago, Ill, Office, oral communication, March 12, 1987). Black children predominated at most ages (Fig 1).

The recorded injury circumstances are shown in Table 1.

Table 2 shows the relationship between victims and perpetrators. Par-

Table 2.—Violent Death in Cook County, Illinois, Younger vs Older Study Cases From 1977 Through 1982: Perpetrator Distribution

Victim Age, y	n	% of Victims in Age Group			
		Only Mother	Any Father	Other	Unknown
<5	292	21	28	21	30
≥5	145	6	4	63	27
All	437	16	20*	35†	29

*Father (8%), stepfather (2%), and/or mother and stepfather (10%).

†Acquainted (21% of all), stranger (8% of all), and/or unspecified (5%).

Table 3.—Violent Death in Cook County, Illinois, From 1977 Through 1982: Incidence Rates*

Age, y	Male and Female, Black and White		County Male and Female		County Black and White	
	County	Chicago	Black	White	Male	Female
<1	16.71	36.74	29.54	7.48	17.79	14.86
1-4	5.47	13.10	10.38	2.05	6.66	4.10
1-2	7.86	19.77	14.74	2.19	10.36	5.13
3-4	3.06	6.35	6.05	1.08	2.93	3.93
5-9	4.22	3.14	2.24	0.59	1.56	1.00
10-14	2.51	6.19	3.93	1.21	3.48	1.45
10-11	2.10	1.62	0.98	0.52	1.02	0.53
12-14	3.63	9.18	5.84	1.65	5.08	2.05

*Violent deaths include homicide and undetermined deaths. Mean annual rates per 100 000 population (<1 year, live births), 1980 census

ents were the predominant perpetrators among victims under age 5 years, in contrast to a predominance of others for children 5 years of age or older ($P<.001$). Among the third of cases with parent perpetrators, fathers were involved in more than half.

Homicide vs Undetermined Cases

Several analyses were done to compare cases of homicide and undetermined manner. Perpetrator distributions differed ($P<.001$ for eight perpetrator categories). Sex distributions by age were not significantly different. When mean ages were compared for homicide and undetermined cases within each circumstance category, these differed only for blunt injury (mean \pm SD: homicide, 2.8 ± 3.7 years vs undetermined manner, 1.2 ± 1.8 years; $P<.01$). In an analysis of variance with age dependent, injury circumstance contributed to the model ($P=.001$), but manner did not ($P=.82$), and there was no significant interaction between manner and injury circumstance ($P=.87$). As these analyses did

not seriously challenge the clinically motivated inclusion of both manners in the study, for the remainder of the report, "violent death" is used to include both homicide and undetermined cases.

Age and Injury Circumstances

The relationship between age and injury circumstance was demonstrated in the analysis described above. In addition, the victim mean age varied substantially for the different injury circumstances. In a pairwise comparison of mean ages for the nine injury circumstances using Scheffé's test, circumstance pairs that did not differ in mean age were considered to be clustered. This analysis revealed a "younger" cluster of circumstances, ie, blunt injury, arson, fall, burn, and neglect/malnutrition, and an "older" one, ie, gunshot, hit-and-run, and strangulation/stabbing. Gunshot deaths accounted for 49% of homicides among 10- through 14-year-old victims (age 10 years: 0%; age 11 years: 50%; age 12 years: 44%; age 13 years: 55%; and age 14 years: 56%).

Epidemiology: Geographic and Demographic Distribution of Homicide Cases

Mean annual age-, race-, and sex-specific rates per 100 000 population for homicide, undetermined manner, and all violent deaths were calculated for Cook County as a whole and for the city of Chicago (Table 3). Rates for the undetermined deaths exceeded those for the deaths that were ruled as homicides through age 4 years. The violent death rates showed a U-shaped distribution with respect to age.

There were large differences in death rates for age subgroups within the standard vital statistics age groupings. For example, Chicago violent death rates were 19.77 for the ages of 1 and 2 years, 6.35 for the ages of 3 and 4 years, 1.62 for the ages of 10 and 11 years, and 9.18 for the ages 12 through 14 years.

Male violent death rates exceeded female rates in most subgroups, and did so uniformly for victims aged older than 4 years. Violent death rates for Chicago were double or more than double those for the county as a whole. Rates for blacks exceeded those for whites, both in Chicago and in the county as a whole. The ratio of black to white homicide rates ranged from a low of 1.0 (for 10- and 11-year-old boys in Chicago) to a high of 10.4 (for 3- and 4-year-old girls in Chicago), with values between 2 and 5.5 for most subgroups.

All the violent deaths were confined to 259 census tracts; 22% of the 1232 census tracts with population in Cook County in 1980. Thus, the great majority of tracts had no violent deaths in the study age ranges. Tract-specific rate ranges varied by age: 0 through 2780 for age less than 1 year, 0 through 930 for the ages of 1 and 2 years, 0 through 480 for the ages of 3 and 4 years, 0 through 280 for the ages of 5 through 9 years, and 0 through 240 for the ages 10 through 14 years. The rate range in each age group was divided into two categories, high and very high, at the median rate for all incidence tracts. Mapping indicated that the areas with very high incidence rates for one age range were not always the same as those with comparably high rates for another age range, with the greatest discrepancies between the youngest and the oldest age groups (Figs 2 and 3: maps for <1 year and 10

through 14 years). Statistical analysis confirmed that the correlation between the younger than 1-year-old rates and the 10- through 14-year-old rates was weak ($r = .12$, $P = .053$).

Comparison of tracts with and without homicides showed that 53% of the 259 incidence tracts had 25% or more of their populations living below the poverty line, compared with 25% of the 893 nonincidence tracts. Multiple linear regression analyses produced extremely weak models relating social/demographic factors and homicide rates. For tract level analysis of infant homicide rates, only 11% of the variance in rates was explained (with child population, poverty, and teen homicide rates contributing to the model); for the 10-through 14-year-old rates, only 5% of the variance was explained (with infant rates, teen population, and crowding contributing). For the community area analyses, the models were even weaker. Thus, although an association between the homicide incidence and poverty was found, no strong demographic correlates of homicide rates in incidence tracts were identified.

Clinical Observations: Details of Fatal Injury Situations

Available information on the most frequent victim groups was used to gain a picture of the situations in which child homicides occur.

Child care at the time of death was known to have been provided by persons other than parents in 26 cases. The ages of these victims ranged from 21 days to 12 years (mean age, 32 months). When the gender of the caretaker was recorded, it was usually male (74%: 17/23). In almost half of the cases in which the perpetrator was identified as a baby-sitter (43%: 10/23) and in the majority of cases where the perpetrator was known to be a male baby-sitter (59%: 10/17), the mother's boyfriend was involved. Almost one third of identified baby-sitter perpetrators (30%: 7/23) were aged younger than 12 years, including several boys (3 of 7). Relatives of unspecified ages, most of them male, constituted one fourth of identified baby-sitter perpetrators (22%: 5/23).

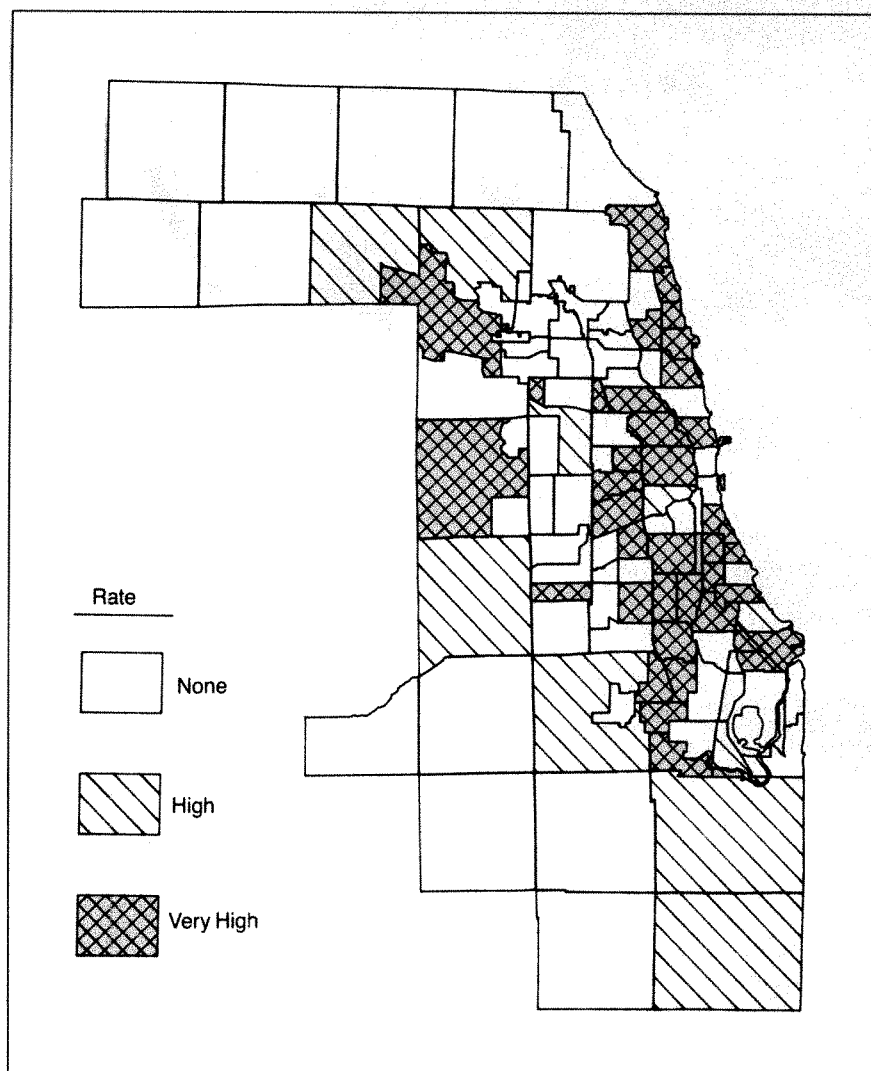


Fig 2. — Violent death distribution by community area: victims aged younger than 1 year.

Incidents that provoked the assault of young children were known in 12 instances: soiling/wetting ($n = 4$), crying ($n = 3$), eating/not eating ($n = 2$), "days and nights reversed" ($n = 1$), other (parents fought in one incident, and "punishment" another). When crying and other incidents were involved, the mean age was 16 months; when soiling/wetting and eating/not eating were involved, the mean age was 41 months.

The situations in which the gunshot deaths occurred are shown in Table 4. Eight (57%) of 14 of the "playing with/or showing a gun" deaths were ruled as of undetermined manner. The mean age varied substantially by situation.

The situations in which the 29 stabbing/strangulation deaths occurred are

shown in Table 5. For the majority (59% [17]), the situation was unknown, including 3 cases in which the bodies were found in dumpsters or garbage cans. When information was available, the situations were characterized by arguments with known persons (3 situations, including 1 concerning \$5), deserted sites (2 situations involved an abandoned building, and 1 involved railroad tracks), intruders ($n = 2$), and cults and related phenomena (eg, "message from God", $n = 3$; there were also 3 cases of dismemberment included in the "other/unknown" injury category that were associated with such phenomena). The age and sex of the victims varied with the situation. The youngest mean age was for cult killings (age, 3 years) and

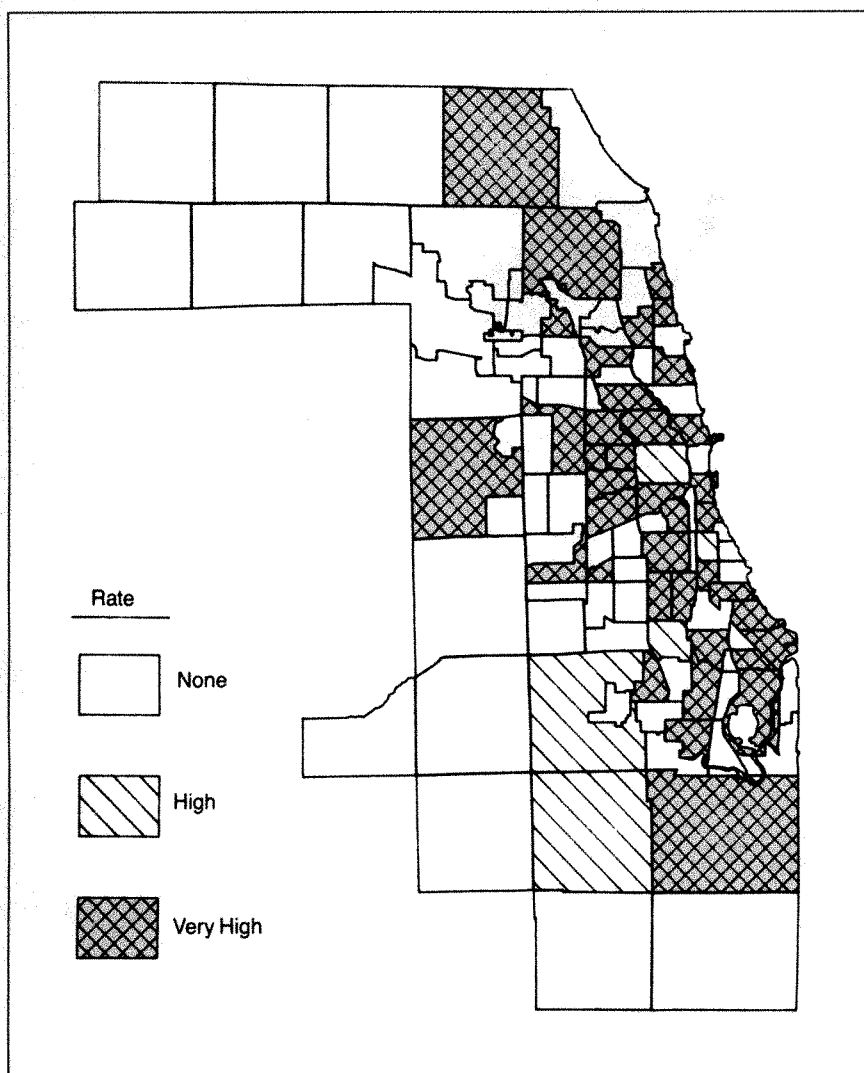


Fig 3.—Violent death distribution by community area: victims aged 10 through 14 years.

the oldest (age range, 12 through 14.8 years) for rapes, deserted sites, and arguments with known persons.

COMMENT Methodologic Considerations

The current report is based on one of the largest and most detailed child homicide data sets thus far studied, derived from death certificates, autopsy reports, and medical examiner records. This is one of several types of data that have been used to obtain information concerning child homicides. Each type of data has advantages and disadvantages.^{22,23} Protective services data are generally detailed, but exclude deaths in which the perpetrators are noncare-takers. These data exclude most older

child victims and younger children who die due to an assault by a stranger. Federal Bureau of Investigation and related data include only cases that involve police, ie, a variable subset of all suspicious child deaths. Vital data depend on the accuracy of the death certificates, which, in turn, depends on the quality of forensic investigation. Many jurisdictions have inconsistent access to trained forensic pathologists, whose child death investigations have set current standards.²⁴

The inclusion of undetermined cases in this study resulted in violent death rates that were virtually *double* the official rates in the younger age groups. It is likely that these higher rates are more nearly correct than the official rates.

Table 4.—Violent Death in Cook County, Illinois, From 1977 Through 1982: Gunshot Deaths: Relationship of Age to Injury Situation

Situation	No. of Deaths	Mean Age, y
Friend/acquaintance	14	13.2
Playing with or showing gun	14	9.8
Gang related	8	12.9
With parent suicide/homicide	7	2.5
Bystanding during gunfire	7	6.9
Associated with other crime	3	14.0
Other ¹	5	9.8
Unknown	14	12.7
All	72	10.5

The higher rates indicate that violent death, particularly in early childhood, is a problem of even greater scope than previous studies (of homicide only) have indicated.^{1,2,4} Some violent deaths, particularly in infancy, are not reported as homicides.^{25,26} Some of these are, usually appropriately, recorded as deaths of undetermined manner. Overestimation of homicide incidence due to data that include undetermined cases can be minimized by exclusion of cases that are unlikely to be violent based on available information, as in this study.

Study Findings

The present study extends our understanding of child homicide. Its results confirm findings of studies that have been done in other areas and locales, and supply needed details concerning age-specific incidence patterns. Findings that confirm the results of other studies include the existence of "younger" and "older" patterns of fatal injury,^{8,5-7,9,12,13,15,16,18} overrepresentation of male^{8,6,7,9,12,13,15,16} and black^{5-7,9,12,13,15} victims (particularly after infancy), association of homicide with urban residence and poverty,^{5,7,13,14-16,18,19} and the role of males as perpetrators.^{9,10,16} These commonalities, along with the type of data used and the fact that the calculated Cook County homicide manner death rates are comparable with 1983 US rates,^{21,27} suggest that the more detailed findings of the present study probably have good

Table 5.—Violent Death in Cook County, Illinois, From 1977 Through 1982:
Strangulation and Stabbing: Injury Situations

Situation	No.	Mean Age, y	M:F Ratio
Unknown	17	7.9	11:6
Rape involved	3	12.0	0:3
Found in dumpster	3	6.4*	2:1
Parent also dead	3†	7.7	2:1
Deserted site‡	3	12.6	1:2
Rape involved§	1	14.8	0:1
Argument with known person	3	13.5	2:1
Intruder	2	6.9	1:1
Other¶	2	5.5	2:0
Cult#	2	3.0	1:1
Total	29	8.0	18:11

*Includes newborn male; mean age of other two children, 9.6 years.

†Includes two siblings.

‡Found near railroad tracks (n = 1) and abandoned buildings (n = 2).

§Blood alcohol level elevated.

||One argument concerned \$5.

¶Smothered to quiet (5-year-old child with urinary infection); disturbed stepmother stabbed multiple family members.

#Three others (included in circumstances *other/unknown*) dismembered in cult situations; mean age, 2.1 years.

generalizability.

Several of the details concern the role of rapid developmental changes during early childhood and adolescence in violent death incidence patterns. These reinforce the notion that violent death patterns in childhood are tightly tied to victim vulnerabilities related to biopsychosocial development,^{7,28} for which age is taken as a proxy. Seasonal patterns of violent death vary with victim age: winter is more dangerous for young children (who get beaten) and summer for older children (who get shot). Analyses using narrow age groupings revealed threefold to fivefold differences in incidence rates in subgroups within standard age groupings. These indicate that standard reporting practices with narrow age ranges must be added to current agendas for improved comparability of data sets.²⁹⁻³²

Age-specific patterns were found not only across but also within injury circumstances. For example, gunshot deaths rose abruptly at the age of 11 years, consistent with earlier analyses.²⁸ The youngest gunshot victims died in association with parental death, and the oldest gunshot victims died in association with peer interactions or crimes.

The study provides not only information but also questions concerning the risks that children face in their commu-

nities. Children of different ages were found to be most endangered in different areas. Census variables did not explain the variation in age-specific death rates across incidence tracts, although such variables account for much of the geographic variation in child abuse incidence.³⁴ Several factors probably contribute to this discrepancy. First, child abuse is more prevalent than child homicide; thus, it involves a much wider range of rates, ie, a more favorable statistical situation for finding a relationship to independent variables. Second, the multivariate analyses in this report are confined to incidence tracts; inclusion of non-incidence tracts would presumably confirm that homicide is closely tied to poverty, as in the bivariate analysis presented. Third, the choice of independent variables may affect results. Finally, there are systematic distortions in abuse statistics that exaggerate the relationship between abuse and poverty.³⁵ Future research will need to address these issues to clarify "the community factor" in child homicide risk.

Implications for Prevention

The consistency between the results of this large, contemporary, and detailed study and previous work suggests that the time has come to move beyond descriptive studies to preven-

tion trials. Observed age-related patterns of violent death suggest specific prevention approaches.

The deaths of very young children were, overwhelmingly, related to neglect or maltreatment by parents and other supervisors. Often, death resulted from violent attempts to deal with difficult but common behaviors of infants and toddlers. In such trying circumstances, the boys, girls, men, and women who provide child care require more or less automatic behavioral repertoires for dealing with their charges: it is difficult to think of options when one is violently angry. Means are therefore needed to provide future child caregivers with this kind of automatic behavioral repertoire. Perhaps doll and role playing, beginning in kindergarten, would protect future children when the kindergartners themselves become child caregivers, often sooner rather than later. Evidence that males are contributing increasingly to serious child maltreatment³⁶ emphasizes the need for boys, as well as girls, to learn to care for infants and toddlers.

The deaths of both male and female preadolescents and adolescents often occurred in situations in which the youngsters apparently failed to appreciate their danger and/or were unable to escape from it. This indicates a need for self-protection skills for boys, as well as girls, although our society generally offers such skills mainly to girls. Means must be found to teach such skills, probably beginning very early in life.

Although educational interventions with potential victims and perpetrators seem to be necessary, it is probably hazardous to rely entirely on such approaches.²⁸ Another prevention goal must be for communities to complement the child care provided by families, as families complement the education, transportation, and recreation that communities offer. The community role should include efforts to ensure young people safe passage through society. Gun control, with its promise of reduced contact by children with the second most common means of child homicide, is a possible starting point.

CONCLUSIONS

The study findings lead to the following conclusions:

1. Separate strategies are needed to protect the two groups at highest risk for violent death: black children aged younger than 3 years and aged older than 11 years in poor urban areas.

2. Standard homicide- and child abuse-reporting practices should include narrow age groupings in childhood and adolescence.

3. Age-related patterns of violent death must be considered in the planning of prevention trials. Enough is known to embark on this difficult enterprise.

4. Research is needed to clarify why children of different ages are at differing risks in different communities.

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Firearm Ownership Among Nonurban Adolescents

Laura S. Sadowski, MD, MPH; Robert B. Cairns, PhD; Jo Anne Earp, ScD

• **Firearm injury is the second leading cause of death among teenagers. In this study we examined firearm acquisition and ownership in a biracial cohort of 664 teenagers (313 male and 351 female). Ownership was prevalent among male adolescents (48%) and rare among female adolescents (4%). Among these suburban and rural teenagers, the ownership rate was highest for white male adolescents (56%). Handgun ownership was more frequent among male school dropouts (22%) than enrollees (7%). The first firearm was typically acquired by late childhood or early adolescence (median age, 12.5 years). An adult male family member (eg, father, grandfather, uncle) was the primary source. The prevalence, developmental timing, and sociodemographic correlates of firearm acquisition should be useful for informing preventive clinical practice and interventions.**

(AJDC. 1989;143:1410-1413)

Firearm-related injuries are the second leading cause of death among 15- to 19-year-olds in the United States.¹ Firearms are involved in the majority of suicides and homicides among 15- to 19-year-olds and the mortality rate for unintentional or "accidental" firearm deaths is highest for this age group.² Morbidity data for firearm-related injuries are less available. Estimates of non-fatal firearm injuries are that for every firearm fatality there are at least five nonfatal injuries.³

An association between firearm availability and firearm-related deaths has

been suggested by ecological studies.^{4,5} In the United States, rates of firearm fatalities increase as rates of firearm ownership increase⁴ and parallel the number of new firearms available for sale.⁵ Studies of individuals have looked primarily at firearm availability among population subgroups, particularly gunshot victims in whom most deaths occurred in the residence where the firearm was kept.^{6,7}

Few studies have looked at firearm availability among adolescents despite the dramatic increase in the rates of firearm-related deaths in the 15- to 19-year-old age group.¹ In Baltimore, Md, a survey of high school students found that almost half the male adolescents carried a handgun and 37% said their parents kept a handgun at home.⁸ In another study, the availability of firearms within the home was higher for adolescents who committed suicide than for adolescents who attempted suicide and failed.⁹

Only modest information is available about the conditions surrounding firearm injury among teenagers, including the key issues of firearm availability and firearm ownership. We report on the behavioral and demographic characteristics of teenagers who own firearms, how and why they came to own them, and the firearm-related injuries they have experienced.

METHODS Cohort

This study was done in the context of a longitudinal research program that tracked a representative sample annually from childhood to early adulthood. The cohort was assembled in 1981 to study social development; its members have been interviewed annually. All fourth and seventh grade public school enrollees in two biracial school districts in a southeastern state were eligible; 70% of the children and their parents agreed to participate in the original study. Nonparticipants were similar to participants in age, sex, race, and school performance. One of the school districts is classified by the US census as

rural and the other suburban. Agriculture, small businesses, and textile and furniture manufacturing provided the predominant economic base in these districts.

Our sample of 664 teenagers represented more than 95% of the original 1981 cohort. Of the 32 teenagers (4.5%) not included, 5 had died and 8 did not give permission to participate; the interview tape for 1 teenager was inaudible, and for the remaining 18 teenagers, the interviewers felt that the conditions were inappropriate for sensitive questioning (eg, court house, history of avoiding interviewers, recent return from drug rehabilitation programs). The 27 living subjects not included were similar in age and socioeconomic status (SES) to other cohort members. However, among these 27 subjects, there were more male adolescents (59% vs 47%), whites (85% vs 75%), and school dropouts (67% vs 11%) than in the study sample.

Interviews

The 664 teenagers were interviewed between February 15, 1987, when the initial set of firearm ownership questions was added to the interview, and July 30, 1988. Firearm acquisition data were obtained from a subgroup of our sample, those teenagers interviewed after November 1, 1987 (ie, when these additional questions were included in the interview) who owned firearms ($n = 116$; 107 male and 9 female).

Thirty- to 60-minute, audiotaped, semi-structured, confidential interviews were conducted by two experienced interviewers. The interview location was usually a private office when the teenager was in school or in a private location at the teenager's job site or home when he or she had dropped out of school.

Variables and Analysis

The associations among firearm ownership and age, sex, race, recreational hunting, school enrollment, and SES were examined. Firearm ownership and acquisition status were determined using teenager self reports. Age, sex, and race were obtained from school records. Hunting was based on the teenagers' reports. School records and teenager reports determined school enrollment status and SES. Firearm mortality data were obtained from medical examiner re-

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The views are those of the authors and do not necessarily reflect those of the Robert Wood Johnson Foundation.

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Table 1.—Ownership of Firearms Among Male Teenagers

Sociodemographic Characteristics	No. (%) of Firearms	No. (%) of Handguns
Race		
B (n = 70)	14 (20)	3 (4)
W (n = 243)	135 (56)*	25 (10)
Age		
<16 y (n = 88)	42 (48)	10 (11)
≥16 y (n = 224)	107 (48)	18 (8)
School enrollment†		
Dropout (n = 41)	22 (54)	9 (22)
Enrolled (n = 250)	115 (46)	17 (7)‡
Hunting experience§		
Past hunter (n = 190)	135 (71)	25 (13)
Never hunted (n = 85)	10 (12)*	3 (4)
Ownership of rifle or shotgun		
Yes (n = 139)	...	22 (16)
No (n = 174)	...	6 (3)*
Mean socioeconomic status score¶	31.9	30.4

* $P < .001$, χ^2 .

†Twenty-two subjects were excluded because of age younger than 16 years.

‡ $P < .01$, χ^2 .

§Thirty-eight subjects are missing.

|| $P < .05$, χ^2 .¶Not significant, owners vs nonowners, using unpaired Student's t test.

Table 2.—Incidence of Firearm Ownership

Characteristic	P	Relationship More Likely If ...	Relative Risk (95% Confidence Interval)
Firearm ownership*			
Sex	<.001	Male	11.7 (5.5-24.8)
Race	.03	White	2.4 (1.1-3.9)
Hunting			
Past	<.001	Ever hunted	4.7 (2.0-10.5)
Current	<.001	Currently hunts	4.4 (2.0-9.0)

*Logistic regression model—age, school enrollment status, and socioeconomic status are not significant.

ports. Firearm morbidity data were obtained from unsolicited teenager reports.

The SES was measured using the Duncan Socioeconomic Index.¹⁰ This multidimensional scale was applied to the reported occupation of each adult living in the teenager's household. The highest SES score within each household was coded.

A firearm was defined as any gun from which a bullet or gunshot was discharged by gunpowder. Rifles, shotguns, and handguns (ie, a firearm held and fired typically with one hand) are subsumed by this definition. Pellet, BB, and air guns were excluded from the analysis. The number and type of all firearms were coded. Firearm ownership was defined as those firearms identified by the teenagers as belonging to them. Ownership of firearms was analyzed dichotomously, whether the teenager owned at least one firearm or owned no firearms. Handgun own-

ership was measured similarly. In addition, the following five self-reported variables measured how the firearm was acquired: the age at acquisition, the type of firearm acquired, the occasion of acquisition, the person who acquired the firearm, and the intended purpose for acquiring the firearm.

All 664 interviews were transcribed verbatim and coded by two research associates. Exclusive ownership of firearms was required; teenagers with firearms that were shared (ie, co-ownership) were not considered firearm owners ($n = 1$). A firearm was not considered a handgun unless it was explicitly described as a "pistol" or "revolver" or had a specific and complete handgun name (eg, "357 magnum"). Intercooder reliability for firearm ownership was .92, using a κ statistic. Test-retest reliability for firearm ownership for the 15 teenagers who were asked the study questions during their 1987

and 1988 interviews was .86, using a κ statistic.

The Statistical Analysis System was used for calculating the Mantel-Haenszel χ^2 test, unpaired Student's t tests, and Fisher's Exact Test statistics (two-tailed) for the bivariate analyses.¹¹ Stratification was used to control for possible confounders. Multivariate analyses for predicting the incidence of ownership of at least one firearm was performed using logistic regression.¹²

RESULTS

Sample Characteristics

The sample consisted of 313 male adolescents (47%) and 351 female adolescents (53%). The mean age (\pm SD) was 17.4 ± 1.7 years (range, 14 to 20 years of age). Seventy-five percent of the adolescents were white and 25% were black; 22% of the population in the counties of the two school districts was black. Eleven percent (69/619) of the teenagers 16 years of age or older had dropped out of school. The mean SES score for our sample was 31.3, slightly lower than the national average of 34.5.¹⁰

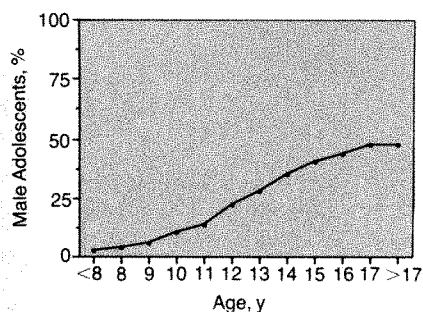
Firearm Ownership

In our sample, 162 teenagers owned 351 firearms. The rate of firearm ownership was 12 times higher among male than female adolescents (149 [48%] of 313 vs 13 [4%] of 351) ($\chi^2 = 172.9$, $P < .001$).

Table 1 summarizes firearm ownership. Among male adolescents, whites had a higher rate of firearm ownership than blacks (56% vs 20%). School enrollment status, SES, and age, within the age ranges of this sample, were not associated with firearm ownership (Table 1).

Male adolescents who hunted owned firearms more often than male adolescents who had never hunted. Prior hunting experience was associated with gender (more male adolescents than female adolescents), race (more whites than blacks), and firearm ownership (more owners than nonowners). When controlling for hunting experience, the racial difference in firearm ownership remained ($\chi^2 = 5.1$, $P < .05$).

In a logistic regression model for firearm ownership, sex, hunting experience, and race were associated with ownership of at least one firearm and explained 46% of the variance observed



Cumulative incidence of firearm ownership among male adolescents

(Table 2). In this model, school enrollment status, SES, and age were not associated with ownership.

Handgun Ownership

The rate of ownership of handguns was nine times higher among male than female adolescents (28 [9%] of 313 vs 5 [1%] of 351) ($\chi^2 = 19.8$, $P < .001$). Male adolescents who dropped out of school were more than three times as likely to own a handgun as those in school (Table 1). Male adolescents who had hunted owned a handgun more often than male adolescents who had never hunted. Handgun ownership among male adolescents was associated with owning other types of firearms; of the 28 male adolescents who owned handguns, 22 (79%) also owned a rifle or shotgun.

Similar to the racial differences found among firearm owners, handgun ownership ($n = 28$) was $2\frac{1}{2}$ times greater among whites than blacks, although statistical significance was not achieved. As was the case with ownership of firearms, SES and age were not associated with ownership of handguns among male adolescents.

In a logistic regression model of the incidence of handgun ownership among male adolescents, only school enrollment status was associated with the ownership of at least one handgun. The relative risk for school dropouts owning a handgun was 3.5 times the risk for enrollees (range, 1.3 to 8.3; 95% confidence interval [CI]).

Ownership Among Female Adolescents

Firearm ownership was rare among female adolescents (4%). Five owned a handgun and 8 owned either a rifle or shotgun. Among the 13 female firearm

owners, handgun ownership and rifle/shotgun ownership were mutually exclusive (ie, no one who owned a handgun owned a rifle or shotgun and vice versa) (Fisher's Exact Test, $P < .001$). Race, SES, and school enrollment status were not associated with firearm ownership among female adolescents. Among all female adolescents, 23% had hunted at least once. As with male adolescents, hunting experience was associated with owning a firearm among female adolescents (Fisher's Exact Test, $P < .001$).

Firearm Acquisition

Information describing the acquisition of firearms was obtained from 107 male adolescents who owned 149 firearms. Among male adolescents, firearms were acquired as a gift by 74%. Firearms were directly purchased by 16% of the male adolescents and inherited by 8%. Fathers were the source of 38% of the firearms, and other male relatives (eg, grandfather, brother, uncle) were the source of 22% of the firearms. When teenagers did not purchase the firearm themselves, the source, when specified, was almost always another man (96%). The reported purpose for acquiring the firearm was predominantly recreation (91%), rather than protection (4%) or adding to a gun collection (2%). The first firearm was usually a shotgun (49%) or a rifle (44%) rather than a handgun (7%).

Among male owners, the mean and median age of acquiring their first firearm was 12.5 years (range, 12.0 to 13.0 years of age, 95% CI); 22% of these teenagers were 10 years of age at the time they first acquired a firearm (Figure). There were no differences found between the age of acquiring the first firearm and the sex, race, hunting experience, SES, or school enrollment status of the owner (Figure).

Firearm Injury

During the course of this longitudinal study, 100% of the original group of 696 teenagers were tracked for a 6-year-period. There were 6 deaths, 3 related to motor vehicle injuries, 1 a suicide from a narcotic overdose, and 2 related to firearms. One subject died after being interviewed. Five male adolescents were involved in serious firearm-related injuries, 4 as victims (3 white, 1

black) and 1 as the perpetrator (white). There were 3 fatal and 2 nonfatal firearm-related injuries. Except for the 1 self-inflicted injury, all of these shootings involved male relatives. There were no firearm injuries among the female adolescents.

COMMENT

Firearm ownership is surprisingly common among particular subgroups of teenagers in this cohort. The majority of the white male adolescents owned firearms, and ownership first occurred during early adolescence. A striking difference in ownership rates appears in comparisons between white male adolescents (56%) and other sex-race categories (20% for black male adolescents, 4% for white female adolescents, and 2% for black female adolescents). The differential participation rates among male and female adolescents in firearm recreational activities (eg, hunting) does not wholly explain the gender differences in ownership. The racial difference in firearm ownership in our cohort may be, in part, due to fewer older men living in the homes of black teenagers¹³ or fewer older black men owning firearms themselves, and, therefore, being less apt to give firearms to other family members. The racial difference in firearm ownership is not due to SES. A statistically significant racial difference in handgun ownership was not found. This may, however, reflect the relatively small number of handgun owners in our sample.

Most firearm owners in this cohort acquired their guns as gifts, usually by early adolescence, and virtually always from an older male family member. This pattern may reflect a value system within these teenagers' families that encourages firearm ownership among male members. The circumstances that surround firearm ownership (ie, the timing of the initial acquisition in early adolescence, older men giving to younger male adolescents, and involvement in hunting, a strongly gender-typed activity) suggest that at least for some male adolescents, ownership plays a normative role during their transition from childhood to maturity. In support of this interpretation, firearms are portrayed as sources of responsibility in the written media, appealing to young boys

(*Boy's Life*, September 1988;78).

Potential limits to the generalizability of these findings deserve comment. This sample of teenagers lived in predominantly rural and suburban locations. Studies of firearm ownership among teenagers in urban settings may show rates different from this study, particularly among black teenagers, the majority of whom reside in urban areas.¹⁴ In addition, the possible influence of regional differences needs to be kept in mind.

These firearm ownership rates rely on self-reported data. In our study the interviewer-teenager relationship developed within a 6-year period to the point where a strong rapport and trust had been created. Teenagers in this study seemed to perceive their responses to these queries as important and confidential. Even so, our firearm and handgun ownership rates are probably an underestimation due to our stringent definitions and coding rules. The 27 teenagers not included were from the subgroup most likely to own firearms (predominantly male, white, and school dropouts).

The vast majority of all firearm deaths occur among household members, relatives, and friends¹⁶; most of the unintentional firearm deaths are within the home.¹⁵ The health threat from firearms is due, in part, to their lethality. Firearm ownership implies access to firearms and a self-determined amount and type of use, although for some teenagers this may depend, in part, on parental supervision, rules, or customs regarding firearms and safety

precautions. The relationship between firearm injury and the availability, accessibility, and use of firearms needs to be investigated further in multiple settings. During the course of this longitudinal study we documented serious firearm injuries in proportions roughly equivalent to the overall rates of firearm ownership found among male vs female adolescents and whites vs blacks. Undoubtedly, there are additional nonfatal firearm injuries that we were unable to identify.

The sheer prevalence of firearm ownership among teenagers demands broader recognition. Moreover, the multiple functions served by such ownership in adolescence need to be better understood. In the light of the present information on ownership prevalence and injury, families would seem likely to benefit from better information on the health hazards and product safety of firearms.

The role of physicians in the prevention of firearm injury, through influencing firearm availability among their patients, is twofold, as educators and advocates. Taking a medical history can provide access to information regarding the availability of firearms among patients. Educating patients on the hazards of firearms in the home can be incorporated into the health maintenance component of office visits. Repetition, reinforcement, and the inclusion of family members in this educational process is important.

Our findings suggest that certain guidelines are needed for the clinical implementation of steps toward the pre-

vention of firearm injuries. Since the majority of these firearms are gifts and men are the primary firearm givers and users within the family, the inclusion and cooperation of male family members seems important. If these individuals are not accessible to the clinician, identifying and including other key family members who could, in turn, influence these male adolescents could be substituted. Including these key influential family members in the patient educational process seems particularly important when dealing with the following: (1) boys in preadolescence or early adolescence, (2) depressed or potentially suicidal patients, and (3) patients and their families during stressful times.

As patient advocates, physicians can individually and collectively support the development and implementation of effective injury prevention programs in the community through workshops, community forums, or public service announcements. Collective action by local and national health professional organizations, as well as local consumer groups, is essential to deal effectively with this health problem. The American Medical Association and the American Academy of Pediatrics are two organizations that have supported legislation aimed at controlling firearm availability and injury.^{16,17}

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Prophylaxis of Recurrent Acute Otitis Media and Middle-Ear Effusion

Comparison of Amoxicillin With Sulfamethoxazole and Trimethoprim

Nicola Principi, MD; Paola Marchisio, MD; Emilia Massironi, MD;
Rosa Maria Grasso, MD; Gianfranco Filiberti, MD

• We compared the efficacy of amoxicillin with that of the combination drug sulfamethoxazole and trimethoprim in reducing recurrences of acute otitis media (AOM) in a single-blind, randomized, placebo-controlled trial involving 96 children. Each of the children had had three or more episodes of AOM in the preceding 6 months, and 97% (93/96) of them still had unilateral or bilateral effusion at the beginning of the study. During the 6-month study period, 9 (27%) of 33 of the children in the amoxicillin group developed 9 episodes of AOM, 9 (27%) of 33 of the children in the sulfamethoxazole and trimethoprim group experienced 11 episodes of AOM, and 19 (63%) of 30 of the children in the placebo group developed 25 episodes. Young age and day-care attendance characterized children for whom prophylaxis was more efficacious. Overall persistence of middle-ear effusion was shorter in treated children only as a consequence of the reduced number of new episodes of AOM. (*AJDC*. 1989;143:1414-1418)

Acute otitis media (AOM) is one of the most common pediatric diseases, characterized by a tendency to recur, especially during the first few years of life.¹⁻³ Recurrences may be clinically important, both because of the morbidity of each acute illness and because of possible long-term sequelae, such as delay in language development and learning disabilities.⁴⁻⁷

Antimicrobial prophylaxis is one of the medical options recommended for the management of this disease.⁸⁻¹³ Several studies have demonstrated the efficacy of various antimicrobial agents, such as the beta-lactam antibiotics (pen-

icillin V, ampicillin, amoxicillin) and sulfonamides.¹⁴⁻²⁴ However, data are lacking on the comparative efficacy of different prophylactic regimens, both in preventing acute episodes and in modifying the outcome of persistent middle-ear effusion.

Our study compares the efficacy of prolonged administration of low-dosage amoxicillin with that of the combination drug sulfamethoxazole and trimethoprim in a group of otitis-prone children.

PATIENTS AND METHODS

The study was conducted between October 1986 and September 1988. Children between the ages of 9 months and 5 years who were attending the outpatient clinic of Pediatric Department IV of the University of Milan (Italy) were enrolled in the study. Each child had had three or more otoscopically and tympanometrically documented episodes of AOM in the preceding 6 months. The last episode occurred between 15 days and 2 months before enrollment. At admission into the study, patients were free of clinical and otoscopic findings of AOM. Excluded from the study were patients who had cleft palate, Down syndrome, immunodeficiency, or a history of allergic reactions to any of the drugs tested. Also excluded were patients who had undergone surgical placement of tympanostomy tubes. Written informed consent was obtained from both parents.

At entry into the study, each patient was assigned randomly to one of three study groups: (1) children receiving amoxicillin, 20 mg/kg per day; (2) children receiving the combination of sulfamethoxazole and trimethoprim, 12 mg/kg per day; and (3) children receiving placebo. Drugs were administered once daily at bedtime in syrup form; the placebo was similar in appearance to one of the active drugs. All of the patients were treated for 6 months.

Patients were examined at entry into the study and subsequently at intervals of 4 to 6 weeks. They also were examined whenever

they developed symptoms of upper respiratory tract illness or symptoms suggesting AOM. At each visit, an interval history was obtained, and a complete physical examination and a tympanometric testing were performed. Pneumatic otoscopy was carried out in each case by the same examiner (P.M.), using a standard otoscope (Welch Allyn model 20200). Tympanograms were obtained with an electroacoustic impedance bridge (Amplifon, model Amplaid 709). The diagnosis of AOM was based on the presence of any combination of fever, otalgia, and irritability and on the presence of hyperemia or opacity accompanied by fullness, bulging, or immobility of the tympanic membrane confirmed by a flat, type B curve. The diagnostic criteria for otitis media with effusion (OME) consisted of the presence of impaired mobility, opacification and either bulging or retraction of the tympanic membrane, associated with a flat tympanogram, and the absence of general or local signs and symptoms of acute infection. Whenever AOM was diagnosed, prophylaxis was discontinued and treatment with cefaclor, 50 mg/kg per day in three doses for 10 days, was prescribed. Bilateral involvement was counted as a single episode. After treatment, if acute signs had subsided, chemoprophylaxis with the original drug was resumed. If acute signs persisted, the study protocol called for tympanocentesis to be performed and another antimicrobial drug to be administered, based on the sensitivity of the isolated pathogen. Tympanocentesis was contemplated only for children with persistent findings of AOM, because of the invasiveness of the procedure and to avoid any possible influence on the course of middle-ear effusion. If another infectious disease requiring antibiotic treatment occurred, prophylaxis was stopped and the more appropriate treatment instituted. Following recovery, prophylaxis was reinstituted. A child was discharged from the study if he or she developed two episodes of AOM within a 2-month period.

At entry into the study, at completion of the third month, and at the end of the treat-

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Table 1.—Characteristics at Entry According to Drug Regimens*

Characteristic	Amoxicillin (N = 33)	Sulfamethoxazole- Trimethoprim (N = 33)	Placebo (N = 30)
Sex			
Male	19 (58)	16 (48)	18 (60)
Female	14 (42)	17 (52)	12 (40)
Age			
9 mo-2 y	16 (48)	14 (42)	13 (43)
2-5 y	17 (52)	19 (58)	17 (57)
Initial otologic status			
Bilateral OME	27 (82)	26 (79)	25 (83)
Unilateral OME	5 (15)	6 (18)	5 (17)
No OME	1 (3)	1 (3)	0
Interval since onset of most recent AOM, d			
15-30	16 (48)	17 (52)	13 (43)
31-60	17 (52)	16 (48)	17 (57)
Season at entry			
October-March	25 (76)	25 (76)	20 (67)
April-September	8 (24)	8 (24)	10 (33)
Day-care attendance			
Yes	18 (54)	21 (64)	16 (53)
No	15 (46)	12 (36)	14 (47)
History of atopy	3 (9)	4 (12)	3 (10)

*Number of patients is followed by percentage in parentheses. OME represents otitis media with effusion; AOM, acute otitis media.

Table 2.—Occurrence of Acute Otitis Media (AOM) During 6-mo Study Period

	Amoxicillin (N = 33)	Sulfamethoxazole- Trimethoprim (N = 33)	Placebo (N = 30)
No. (%) of patients with AOM	9 (27)	9 (27)	19 (63)*
No. of episodes of AOM	11	9	25
Mean No. of episodes per patient	0.33	0.27	0.83
Mean No. of episodes per patient-month	0.06	0.05	0.14

*In the comparison of amoxicillin vs placebo and sulfamethoxazole-trimethoprim vs placebo, $\chi^2 = 6.88$; $P < .01$. In the comparison of drug groups combined vs placebo, $\chi^2 = 9.85$; $P = .002$.

ment period, a blood sample was taken from each patient for determination of hematologic, renal, and hepatic factors to detect drug toxicity. Leukopenia was defined as a total white blood cell count of $4.0 \times 10^9/L$ or less, neutropenia as a polymorphonuclear neutrophilic leukocyte count of $1.5 \times 10^9/L$ or less, anemia as a drop in the hemoglobin level of 20 g/L, and thrombocytopenia as a platelet count of less than $150 \times 10^9/L$.

Compliance with the study regimen was encouraged by asking parents to affix a written reminder of the protocol to the refrigerator door. Parents also were asked to bring the medication bottles with them at follow-up visits, and compliance was evaluated on the basis of the amount of medication remaining in the bottle. Failure to administer three or

more doses was considered poor compliance.

The occurrence rate of AOM was calculated as episodes per patient-month during the study period. The finding of OME in the same ear on two consecutive examinations was considered indicative of the persistence of OME in this ear during the intervening period. The same criterion was adopted for ears without OME. When OME was present on one examination and absent on the next, or vice versa, effusion was considered to have been present during half of the interval, that is, 2 to 3 weeks (in case of fractions, the value in weeks of effusion was rounded to the nearest unit).

All statistical tests were two-sided. Proportions were compared using the χ^2 test with Yates' correction for fourfold tables,

unless the sample was too small ($N = 33$), in which case Fisher's Exact Test was used. Mean values were compared using the Student t test. A stepwise logistic regression analysis²⁵ was used to investigate whether, in addition to the method of treatment, age, sex, season at entry, or day-care attendance influenced outcome, and whether there were interactions between any of these latter subject characteristics and the method of treatment.

RESULTS

A total of 100 children entered the study. Thirty-four were assigned to the amoxicillin group, 33 to the sulfamethoxazole and trimethoprim group, and 33 to the placebo group. Table 1 shows pertinent characteristics of the children at entry into the study. No statistically significant differences in these characteristics were found between the three treatment groups. One child in the amoxicillin group and 3 in the placebo group did not return for follow-up visits and were therefore withdrawn from the study. The remaining 96 were evaluated fully. The entire period of prophylaxis was completed by all of the children in the amoxicillin group (198 of 198 child-months). Children in the sulfamethoxazole and trimethoprim group completed 196 (99%) of 198 of the child-months, prophylaxis having been arbitrarily discontinued after 5 months in 2 children. Children in the placebo group completed 175 (97%) of 180 of the child-months; 1 child was treated with amoxicillin after 2 months because two episodes of AOM developed within 6 weeks, and this patient was retained in the placebo group only for the purpose of analysis of data concerning AOM and not for OME. In 1 child, placebo was arbitrarily discontinued after 5 months.

Table 2 shows data on the occurrence of episodes of AOM in the three treatment groups. In the amoxicillin group, 9 of 33 children developed 11 episodes of AOM; in the sulfamethoxazole and trimethoprim group, 9 of 33 experienced 9 episodes; and in the placebo group, 19 of the 30 children developed 25 episodes (1 child had 3 episodes, and 4 children had 2 episodes each). These differences between the drug groups and the placebo group in the proportions of children who developed AOM were statistically significant ($P < .01$). In each group there was a substantial reduction in the rate of

occurrence of AOM compared with the 6-month period before treatment, during which time each child had at least 0.5 episode per child-month. Thus, the mean rate fell from 0.52 to 0.06 in the amoxicillin group, from 0.57 to 0.05 in the sulfamethoxazole and trimethoprim group, and from 0.52 to 0.14 in the placebo group. No child underwent tympanocentesis because all the cases of recurrent AOM resolved on treatment with cefaclor. Seven (64%) of 11 of the episodes in the amoxicillin group developed during the first 3 months of prophylaxis, compared with 4 (44%) of 9 in the sulfamethoxazole and trimethoprim group and 20 (80%) of 25 in the placebo group. Two episodes in the sulfamethoxazole and trimethoprim group developed in children in whom the drug had been discontinued arbitrarily.

Table 3 shows data on the occurrence of AOM in the various epidemiologic subgroups. Consistently across subgroups, the rate of occurrence of AOM was lower in children receiving either amoxicillin or sulfamethoxazole and trimethoprim than in children receiving

placebo, but the difference reached statistical significance only in certain of the subgroups. The stepwise logistic analysis demonstrated that no statistically significant interactions were present among any of the subject characteristics and the method of treatment. Of the subject characteristics other than method of treatment, only day-care attendance influenced outcome; children attending day care had statistically significantly better outcomes than children not attending.

Table 4 shows data on the season of occurrence of AOM in relation to the season at entry. Irrespective of the season at entry and treatment group, a substantial proportion of all episodes of AOM (40% overall) occurred between April and September. Overall, the mean number of episodes per child appeared independent of the period of entry.

By the end of the 6-month study period, the persistence of OME in each treatment group had declined: OME was present in 51.5% (14/33) of the amoxicillin-treated children (39.4%

[13/33] bilateral, 12.1% [4/33] unilateral); 48.4% (15/31) of the sulfamethoxazole and trimethoprim group (35.5% [11/31] bilateral, 12.9% [4/31] unilateral); and 58.6% (17/29) in the placebo group (44.8% [13/29] bilateral, 13.8% [4/29] unilateral). The differences are not statistically significant. Data on the duration of effusion are shown in Table 5. The total duration of effusion, evaluated as total number of patient-weeks with OME, as well as number of patient-weeks with bilateral OME, was statistically significantly shorter in children treated both with amoxicillin and with sulfamethoxazole and trimethoprim compared with those treated with placebo. However, when children with recurrent AOM are not considered but only children who did not develop AOM are taken into account, the difference in total duration of OME among the three groups is no longer significant.

There was no laboratory or clinical evidence of toxic side effects due to treatment with amoxicillin or sulfamethoxazole and trimethoprim; in particular, we did not find any patient with hematologic abnormalities. The compliance was good in 97% (32/33) of children treated with amoxicillin, in 94% (31/33) of those receiving sulfamethoxazole and trimethoprim, and in 97% (29/30) of children who received placebo.

COMMENT

In recent years, several studies have been performed to evaluate the efficacy of antimicrobial prophylaxis in preventing recurrences of AOM in otitis-prone children. In most of the studies, antimicrobials were prescribed during cold-weather months or concomitantly with upper respiratory tract infections.¹⁴⁻²⁴ However, it is well known that in otitis prone children, "AOM does occur, albeit with reduced frequency, during the summer" as well.¹³ We therefore decided to enroll in the study all the children

Table 3.—Occurrence of Acute Otitis Media in Relation to Epidemiologic Factors*

Characteristic	Amoxicillin (N = 33)	Sulfamethoxazole- Trimethoprim (N = 33)	Placebo (N = 30)
Age			
9 mo-2 y	6/16 (37.5)	3/14 (21.4)	10/13 (76.9)†
2-5 y	3/17 (17.6)	6/19 (31.6)	9/17 (52.9)
Sex			
Male	6/19 (31.6)	6/16 (37.5)	10/18 (55.5)
Female	3/14 (21.4)	3/17 (17.6)	9/12 (75.0)‡
Season at entry			
October-March	7/25 (28.0)	7/25 (28.0)	12/20 (60.0)
April-September	2/8 (25.0)	2/8 (25.0)	7/10 (70.0)
Day-care attendance			
Yes	3/21 (14.3)	3/18 (16.7)	11/16 (68.8)‡
No	6/12 (50.0)	6/15 (40.0)	8/14 (57.1)

*The number of children with acute otitis media was compared with the number of children characterized by each factor. The number in parentheses is the percentage.

†In the comparison of sulfamethoxazole-trimethoprim with placebo, $P = .01$.

‡In the comparison of amoxicillin vs placebo and sulfamethoxazole-trimethoprim vs placebo, $P < .02$.

Table 4.—Occurrence of Episodes of Acute Otitis Media According to Seasons

Season at Entry	No. of Cases	Season of Occurrence						Total No. of Episodes
		October-March			April-September			
		Amoxicillin	Sulfamethoxazole-Trimethoprim	Placebo	Amoxicillin	Sulfamethoxazole-Trimethoprim	Placebo	
October-March	70	5	5	11	4	2	6	33
April-September	26	1	1	4	1	1	4	12

Table 5.—Duration of Effusion According to Drug Regimens*

	Amoxicillin (N = 33)			Sulfamethoxazole-Trimethoprim (N = 33)			Placebo (N = 29)		
	Unilateral	Bilateral	Total	Unilateral	Bilateral	Total	Unilateral	Bilateral	Total
All patients	17.5† (150/858)	50.3† (432/858)	67.8† (582/858)	20.5‡ (174/850)	43.8‡ (372/850)	64.2‡ (546/850)	12.1 (91/749)	63.0 (472/749)	75.2 (563/749)
Patients who developed AOM	18.6† (47/253)	58.9† (149/253)	77.5 (196/253)	16.6 (39/235)	57.4‡ (135/235)	74.0‡ (174/235)	11.2 (53/473)	69.8 (330/473)	81.0 (383/473)
Patients who did not develop AOM	17.0 (103/605)	46.8 (283/605)	63.8 (386/605)	21.9 (135/615)	38.5 (237/615)	60.5 (372/615)	13.8 (38/276)	51.4 (142/276)	65.2 (180/276)

*The number represents the percentage of total patient-weeks with otitis media with effusion (OME) (in parentheses, the number of patient-weeks with OME/the total patient-weeks). AOM indicates acute otitis media.

†In the comparison of amoxicillin vs placebo, $P < .05$.

‡In the comparison of sulfamethoxazole-trimethoprim vs placebo, $P < .05$.

with three documented episodes of AOM during the preceding 6 months, independent of the season in which they came to our observation.

Previous studies used mostly sulfonamides and, in only a few patients, aminopenicillins as prophylactic drugs. On the other hand, it has been demonstrated that in most patients recurrences of AOM are caused by the same bacterial agents commonly found in middle-ear fluid during the first episode of AOM.²⁶⁻²⁸ Therefore, we deemed it reasonable to select for prophylaxis amoxicillin and sulfamethoxazole and trimethoprim, which are usually considered among the drugs of choice for treatment of AOM.²⁹⁻³¹

Our data indicate that amoxicillin and sulfamethoxazole and trimethoprim administered at bedtime in low dosage for 6 months are equally effective, and superior to placebo, in reducing the occurrence of AOM in otitis-prone children. While prophylaxis is certainly more effective than placebo, the relatively small number of children enrolled in the study does not allow us to draw firm conclusions concerning the apparent equivalence of the two prophylactic regimens. Our study has the power to detect a 45% difference between the two drugs: lower differences might be detected only studying hundreds of patients. However, if we divide our population into two age subgroups, efficacy is statistically significant only for sulfamethoxazole and trimethoprim treatment in children up to 2 years of age, even if amoxicillin in both subgroups and sulfamethoxazole and trimethoprim in older children reduces from two to three times the incidence of recurrences

if compared with placebo. Our data agree strongly with those published by Perrin et al¹⁵ and Varsano et al,²² emphasizing the importance of chemoprophylaxis in younger children, and suggest the hypothesis that chemoprophylaxis could be more efficacious in children characterized by one or more of the known risk factors for recurrent AOM. In this way we could also explain the finding that chemoprophylaxis is more effective in children attending a day-care center compared with those cared for at home. Younger age and day-care attendance have, in fact, been demonstrated to be among the most important risk factors for recurrent AOM.³²⁻³⁴ Conversely, season at entry into the study did not seem to play a significant role in the efficacy of prophylaxis; this seems to sustain the possibility that AOM can recur throughout the year and that, after identification of the otitis-prone child, prophylaxis should be started at once. Finally, it is difficult to interpret the fact that prophylaxis is more efficacious in girls.

Concerning the effect of antimicrobial prophylaxis on the persistence of OME, our data suggest that prophylaxis may reduce the cumulative duration of effusion by decreasing the number of new episodes of AOM, but it does not otherwise affect the natural course of OME. In this respect our data amplify those published by Liston et al,¹⁸ who reported that sulfonamide prophylaxis improved the tympanogram pattern in children with recurrent AOM, and by Schwartz et al,¹⁷ who reported reduced occurrence of both AOM and OME. Those studies, however, did not differentiate children who continued to have

recurrent AOM during the study period from those who remained free of AOM. Because effusion often persists for many weeks after an episode of AOM, especially in younger children,^{6,31} it seems reasonable to anticipate that children treated with antimicrobial prophylaxis, having fewer recurrences of AOM than placebo-treated children, would also have shorter cumulative duration of OME. When we evaluated only children without recurrences of AOM, we found that the overall durations of effusion did not differ significantly between the three treatment groups.

On the basis of the data presented in this article, it seems reasonable to recommend the administration of chemoprophylaxis to otitis-prone children, especially if they are younger than 2 years of age and attend a day-care center. On grounds of safety, amoxicillin can be considered the first-choice drug, particularly in areas like Italy, where the problem of β -lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis* is still limited. The combination drug sulfamethoxazole and trimethoprim can be used in children with known allergy to β -lactam antimicrobials or in areas in which the incidence of amoxicillin or pathogens resistant to sulfonamides is increasing rapidly. Both drugs appeared to be well tolerated and safe. In particular, we did not experience any of the most troublesome adverse effects reported both with amoxicillin and with sulfamethoxazole and trimethoprim. The safety of sulfamethoxazole and trimethoprim given at low dosage has been reported in several studies on the prophylactic treatment of recurrent uri-

nary tract infections.^{35,36} Because new episodes of AOM continued to occur, especially in the placebo group, between April and September, we suggest that the duration of the chemopro-

phylaxis be a minimum of 6 months, irrespective of the season of the year in which it is instituted. Once-daily administration at bedtime was well accepted and afforded good compliance and may

be preferable to the twice-daily administration proposed by some authors.^{11,37}

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Predictors of Trough Serum Gentamicin Concentrations in Neonates

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• Neonates admitted to an intensive care nursery frequently receive gentamicin sulfate therapy. This study was undertaken to determine predictors of an elevated (≥ 2 mg/L) trough serum concentration of gentamicin sulfate (undesirable because of potential toxic effects). A total of 140 infants with birth weight of 496 to 4545 g and gestational age of 23 to 42 weeks who received gentamicin in the first days of life were studied prospectively. The trough serum concentration of gentamicin was not significantly affected by concurrent use of dopamine hydrochloride, indomethacin, furosemide, or umbilical artery catheters. Of 11 infants weighing between 1000 and 1500 g on an 18-hour dosing interval, 55% had trough serum gentamicin concentration of 2 mg/L or more. Use of the recommended 24-hour dosing interval for infants weighing less than 1000 g and an 18-hour schedule for preterm infants weighing more than 1000 g resulted in a significant number of elevated trough serum gentamicin concentrations in the latter. A dosing interval of 24 hours for infants less than 1500 g and 18 hours in infants between 1500 and 3250 g is suggested.

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Gentamicin sulfate, an aminoglycoside, is used frequently in neonates to treat suspected or proved infections caused by gram-negative organisms.¹ The use of aminoglycosides also improves the antibacterial activity of penicillins against group B streptococci, *Listeria* organisms, staphylococci, and other bacterial pathogens of newborn

infants.² A peak serum concentration of 4 mg/L has been suggested as a minimum inhibitory concentration for most susceptible gram-negative organisms.¹⁻⁶ Hence, a peak serum concentration of 4 to 8 mg/L is considered to be in the therapeutic range,¹ and a concentration more than 10 mg/L is considered toxic.³

It is recommended that the trough serum concentration, determined before gentamicin administration, be maintained at less than 2 mg/L to prevent toxic effects.^{1-5,7-9} Information is scarce concerning use of the trough concentration to assess toxicity. Assael et al⁶ used 1 mg/L as an indication of possible gentamicin accumulation. Matzke et al⁸ set a lower limit of 0.5 mg/L and stated that this was an arbitrary value to prevent subtherapeutic dosing. Although disagreement exists about whether the peak or trough concentration is a better indicator of toxicity, Jolley et al¹⁰ stated that the trough serum concentration rather than the peak concentration offers a more discrete indication of acute toxicity as the trough serum concentration correlates more closely with tissue accumulation.

In adults, gentamicin has the potential of causing ototoxicity and nephrotoxicity. This cause of toxicity remains a controversial issue in neonates due to the limited number of studies available. Nephrotoxicity usually starts with damage to the proximal renal tubules, resulting in acute tubular necrosis characterized by increased excretion of β_2 -microglobulin, proteinuria, and urinary tubular casts. Later increases in serum creatinine and urea nitrogen concentrations occur.¹¹ However, the injury can usually be reversed with discontinuation of the drug.

Ototoxicity can result in loss of equilibrium, loss of hearing, or both. Early hearing damage can potentially be reversed if the gentamicin treatment is

discontinued; however, recovery of the vestibular apparatus is less likely.²

Because of potential toxic effects, the serum gentamicin concentration should be monitored and the dose adjusted to maintain a trough concentration of less than 2 mg/L and a peak concentration between 4 and 8 mg/L.¹ Variability in serum drug concentration is not unexpected in patients in the neonatal intensive care unit due to inconsistency in drug clearance, associated illnesses, complications, and the effects of other drug therapies received by these infants.

The recommended dose of gentamicin for full-term infants is 2.5 mg/kg every 12 hours.^{1,6} Pharmacologic studies of Szefer et al⁵ and Zarowitz et al¹² have shown that a large number of preterm infants have a high trough serum concentration unless the dosing interval is lengthened.

The protocol for gentamicin administration in our nursery provides for a longer dosing interval for very low-birth-weight infants (ie, those weighing <1500 g). However, our observation of an undesirable number of elevated trough concentrations that required a further modification of the standard protocol schedule prompted us to undertake this prospective investigation.

The objectives of this study were (1) to evaluate the current protocol in minimizing toxic serum drug concentration while maintaining an appropriate therapeutic concentration; (2) to determine predictors (eg, gestational age and birth weight) for peak and trough serum gentamicin concentrations; and (3) to determine the influence of furosemide, dopamine hydrochloride, and indomethacin, which are often used concurrently with gentamicin sulfate in the first days of life of the premature infant, on the occurrence of an elevated trough concentration.

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PATIENTS AND METHODS

Patients

The study subjects consisted of all infants admitted to the Special Care Nurseries, Hospital Corporation of America Wesley Medical Center, Wichita, Kan, who received intravenously administered gentamicin within the first hours of life and had peak and trough serum levels determined. Infants with confirmed congenital renal anomalies were excluded from the study. Data were collected from November 1, 1987, to January 13, 1988. The protocol was approved by the Institutional Review Board at Hospital Corporation of America Wesley Medical Center.

Study Protocol

The protocol for gentamicin sulfate administration during the study period was a dose of 2.5 mg/kg with a dosing interval of 24 hours for infants weighing less than 1000 g. Infants weighing between 1000 and 1500 g were prescribed a dosing interval of 18 or 24 hours; infants weighing more than 1500 g were prescribed an interval of 12 or 18 hours, with the attending physician making the decision as to which interval was used. Birth weights in the three groups ranged from 496 to 1282 g, 948 to 4545 g, and 1494 to 4355 g for 24-, 18-, and 12-hour dose intervals, respectively.

Gentamicin sulfate was administered through a peripheral vein. It was mixed in a dextrose-water solution (the same concentration as the infant's intravenous fluid) and infused through extension tubing for a period of 1 hour using an infusion pump.

Trough serum samples were collected 15 minutes before gentamicin administration, and peak serum samples were collected 1 hour after the infusion was complete. Serum samples were collected routinely with the fourth dose; however, some were collected with the second to fifth dose (mean = 3.8) as ordered by the staff physicians. Samples were collected from umbilical artery catheters, from radial arterial catheters, or by heel stick.

The serum gentamicin concentration was determined by fluorescence polarization immunoassay technology and competitive binding immunoassay method. The CV was 5% at 2.0 mg/L and 3.8% at 5.06 mg/L.

Information gathered from the patient's chart consisted of birth date, time, and weight, and gestational age (using the modified Dubowitz scale); gentamicin dose and dosing interval; date and time of blood sample collection; urine output for the 24-hour period before sample collection and most recent serum creatinine concentration; the presence of an umbilical artery catheter; and concurrent treatment with furosemide, dopamine, and/or indomethacin.

Statistical Analysis

Data were analyzed by factorial one-way analysis of variance (ANOVA) and multiple regression. These two methods yield similar results, are based on the same general linear model, and follow essentially the same assumptions.¹⁸ Analysis of variance was used to demonstrate mean differences first in trough concentrations and second in peak concentrations between the three treatment intervals (a larger sample size would allow a more robust test of group differences). Multiple regression analysis was performed to predict mean trough or peak serum concentration (criterion measure) based on combinations of birth weight, treatment interval, age in hours when measured, dose number, total amount of gentamicin given, creatinine level, urine output, umbilical artery catheter, and administration of furosemide, dopamine, or indomethacin (predictor variables).

Multiple regression analysis followed two steps: first, commonality analysis was used to determine which independent variables were adequate predictors of gentamicin concentration, and second, predictions were made based on regression equations obtained by a forward and backward stepwise solution using a strict F test to enter and remove variables. This procedure resulted in a subset of variables that maximally correlated with trough gentamicin concentration, maximizing accuracy of prediction and raising the subjects to variables ratio beyond the 10:1 ratio needed.

Furthermore, we were interested in the probability that infants with given characteristics (eg, birth weight, creatinine level, urine output, treatment interval) would have a toxic trough gentamicin concentration. Several approaches to selecting a subset of predictors that maximize the probability of this occurrence were possible. Stepwise logistic regression can be used with discrete or mixed discrete-continuous predictors, although multiple regression can also be used if discrete variables are recoded as vectors. In this study, we "dummy-coded"^{14,15} discrete variables to create vectors such that, in any given vector, membership in a given group or category was assigned a variable of 1, while nonmembership was assigned 0. Coding for treatment groups required two ($k-1$) vectors—vector 1, the 18-hour dose interval, and vector 2, the 12-hour dose interval. The vector 1 and 2 variables for the 12-hour dose group were 0 and 1, respectively; for the 18-hour dose group, 1 and 0, respectively; and for the 24-hour dose group, both were 0.

The principle problem with stepwise multiple regression in predictive models is that different orders of entry and removal of predictors into the regression equation may produce notable differences in the relation of each predictor to the criterion measure.

Variable selection becomes less problematic when preceded by commonality analysis, which determines the unique variance of each predictor (or set of predictors) with the criterion measure. Unique variance is the variance associated with a predictor when it is entered into the equation last; in other words, it is the squared, semipartial correlation between the criterion and predictor variable of interest after the partialing of all the predictors from it. Commonality analysis explains the relative predictive power of the regressor variables and determines their usefulness as predictors, guiding subsequent multiple regression analysis.¹⁵

The multiple regression equation has the following form: $Y' = a + b_1X_1 + b_2X_2 + \dots + b_pX_p$, where X_1, \dots, X_p are the predictors used to provide a least-squares estimate of the criterion measure (Y'). The variable Y' is in fact an estimate of the mean Y score of all individuals with a given combination of X_1, X_2, \dots, X_p scores.^{14,15} Since Y' is a mean, we can calculate the probability that an individual's predicted score does not fall below some specified cutoff score (Y^*) by converting Y to a z score: $(z = Y - Y')/s_{y|x}$, where $s_{y|x}$ is the SE of estimate of the regression equation. In other words, the resulting z score expresses the relation of the SE of estimate to the cutoff and predicted gentamicin concentration (ie, its probability of falling below the cutoff). Calculating probabilities in this fashion requires that the variables be multivariate normal.

Calculating the "best guess" estimate of trough serum gentamicin concentration from the regression equation $Y' = 1.85 - 0.000486$ (grams of birth weight) $+ 0.779$ (18-hour interval) $+ 1.669$ (12-hour interval) is as follows for a 2000-g infant on an 18-hour treatment schedule: $Y' = 1.85 - 0.000486(2000) + 0.779$ (coded 1) $+ 1.669$ (coded 0), thus $Y' = 1.657$ (nontoxic concentration).

If we assume that 2.0 mg/L is the cutoff for a toxic trough, the resulting z score is $(2.0 - 1.657)/0.538 = 0.638$. Since a z score of 0.638 cuts off 0.2611 of the area under the gaussian curve with a mean of 2.0, the probability of toxicity for this infant is .2611.

RESULTS

Demographic characteristics of the infants grouped by gentamicin dosing interval (12, 18, and 24 hours) are shown in Tables 1 and 2.

Peak Gentamicin Concentration

All but six (96%) of the infants had a peak serum gentamicin concentration between 4 and 8 mg/L. Five of the six had a peak serum concentration below

Table 1.—Mean Gestational Age, Birth Weight, and Renal Function by Treatment Group*

Characteristic	Treatment Group		
	12-h Interval (n = 77)	18-h Interval (n = 49)	24-h Interval (n = 14)
Gestational age, wk	36.3 (30-42)	33.1 (27-43)	27.4 (23-29)
Birth weight, g	2685.2 (1444-4365)	1899.0 (948-4545)	926.8 (496-1188)
Postnatal age, h†	44.3 (16.5-163.8)	61.2 (36.8-255)	61.8 (48-75)
Total drug dose, mg‡	18.2 (1.2-31.5)	13.4 (3.9-33)	5.5 (2.5-9)
Hourly urine output, mL/kg	4.4 (0-9)	4.5 (.81-9)	4.5 (1.4-10)
Creatinine level, μ mol/L	180 (30-800)	160 (40-800)	90 (50-130)

*Numbers indicate mean values with ranges in parentheses.

†Age when trough serum samples were drawn.

‡Dose indicates the total amount of drug received when trough serum samples were drawn.

4.0 mg/L; these five infants were of higher birth weight in the 18-hour dose group (mean birth weight of 3148 g [range, 1937 to 4545 g], compared with mean birth weight of 1899 g [range, 948 to 4545 g] for the entire group). One infant had a toxic peak serum concentration; however, in reviewing the chart, the peak was determined too early (just after the infusion was completed). The ANOVA indicated no difference in the mean peak concentration between the treatment groups ($P = .0598$). Stepwise multiple regression indicated that the only predictor of peak gentamicin concentration was trough concentration, which accounted for 27.5% of the variance in peak concentration ($r = .524$, $R^2 = .275$).

Trough Gentamicin Concentration

Table 3 shows the prevalence of an elevated trough serum gentamicin concentration in the three study groups.

When the patients were divided by dose interval, ANOVA indicated significant differences in the mean trough concentration between the three groups ($P < .0001$). Post hoc analysis with Fisher's Exact Test of least significant difference indicated that the mean trough serum concentration for the 12-hour dose interval was significantly ($P = .01$) greater than either the 18- or 24-hour mean trough serum concentration.

Commonality analysis, using trough serum gentamicin concentration as the dependent variable, indicated that only three variables (birth weight, 12-hour interval, and 18-hour interval) contained sufficient variance to be used as predictors of trough serum concentration; together they accounted for 36.5%

Table 3.—Observed Frequency of Elevated Serum Gentamicin Trough Concentration for the 12-, 18-, and 24-Hour Treatment Intervals

Birth Weight Range, g	Dose Interval, h	N	Trough Concentration*	
			>2 mg/mL	<2 mg/mL
1494-4355	12	77	50 (65)	27 (35)
948-4545	18	49	19 (39)	30 (61)
496-1282	24	14	1 (7)	13 (93)
Total		140	70	70

*Percent of total is given in parentheses.

of the variance (Table 4). Gestational age was excluded from the analysis due to its correlation of .88 with birth weight.

Subsequent stepwise multiple regression resulted in a highly significant ($P < .0001$) regression equation ($r = .64$, $R^2 = .41$, SE of estimate = .538). The raw score formula for predicting gentamicin trough is $1.85 - 0.000486$ (grams of birth weight) + 0.779 (18-hour interval) + 1.669 (12-hour interval). Probability estimates of toxic vs nontoxic treatment outcomes from this equation are presented in the Figure.

As indicated by their small unique variances (Table 4), variables other than birth weight and treatment interval contributed little to the prediction of the trough concentration. There was no statistically significant relationship between urine output and elevated trough serum gentamicin concentration in our study infants whose hourly urine output varied from 0.71 to 7.29 mL/kg. Fifty-one patients had umbilical artery catheters placed as "high" catheters positioned between T-6 and T-10 (standard placement for our nursery). Our data showed a small but nonsignificant increase in trough concentration associ-

Table 2.—Number of Study Infants in Each Treatment Group Receiving Therapies Potentially Affecting Serum Gentamicin Concentration

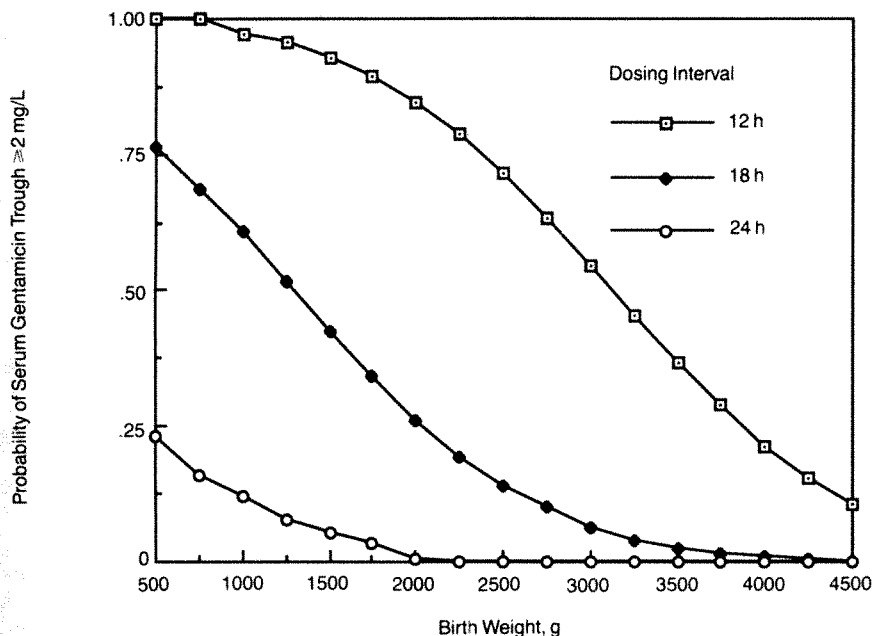
Treatment	Treatment Group		
	12-h Interval	18-h Interval	24-h Interval
Umbilical artery catheter	19	23	9
Furosemide	3	3	2
Dopamine	6	6	6
Indomethacin	1	9	9

Table 4.—Summary of Commonality Analysis Unique Variance Associated With Predictors of Trough Gentamicin Concentration*

Independent Variable-Predictor	% Unique Variance
Birth weight	6.91
Treatment interval	
18-h	6.93
12-h	22.67
Age	0.02
Dose no.	0.17
Total amount of gentamicin sulfate	1.40
Creatinine level	0.27
Urine output	0.00
Umbilical artery catheter	1.19
Furosemide	0.83
Dopamine	0.22
Indomethacin	0.00

*Unique variance refers to the proportion of variance in trough gentamicin concentration accounted for by any single independent variable-predictor.

ated with this umbilical artery catheter placement ($P > .1$). Nineteen infants received indomethacin therapy; 18, dopamine therapy; and 8, furosemide therapy. Ten infants received a combination of indomethacin and dopamine therapy, and 4 infants received a combination of all three drugs. Each drug was evaluated separately; none was found to cor-



Probability of toxic serum gentamicin trough (≥ 2 mg/L) based on birth weight and dosing interval.

relate (ie, predict) an elevated trough serum gentamicin concentration.

COMMENT

Aminoglycosides are bactericidal and produce their antimicrobial effects by penetrating bacterial cell walls and becoming irreversibly bound to the 30s unit of ribosomes in the cytoplasm.³ At this site, they inhibit protein synthesis, which leads to a misreading of the genetic code and to cell death.^{2,3,9}

Aminoglycosides are all nearly identical in their absorption, distribution, and excretion. Aminoglycosides are lipophobic and minimally protein bound; therefore, they are distributed mainly in extracellular fluid.⁸ They are bound to kidney tissue and taken up and concentrated in the renal cortex,¹⁰ where they are slowly excreted from tissues (average gentamicin half-life is 112 hours from renal parenchyma compared with 2 to 3 hours from serum¹¹). The extent to which the drug accumulates seems to correlate with nephrotoxicity.¹¹ It is this potential for causing nephrotoxicity, as well as ototoxicity, that requires frequent monitoring of serum gentamicin concentration.

The recommended sampling time for peak serum concentration is 30 to 60 minutes after an intravenous infusion and 30 to 90 minutes after intramuscular injection.¹¹ This allows for ample distri-

bution of the drug to the tissues. Hindmarsh et al,¹ Mulhall et al,⁴ Szefer et al,⁵ and Zarowitz et al¹² used the level determined 1 hour after gentamicin administration as the peak concentration, and it has been the routine sampling time in our nursery.

Gentamicin clearance is decreased in renal failure, and the dosing interval schedule must be modified to avoid accumulation that may lead to toxicity. We had anticipated that urine output and creatinine level would serve as predictors of gentamicin concentration. However, their power to do so was low. An explanation for this may be that few infants were actually oliguric (<1 mL/kg per hour), and none was severely oliguric (<0.5 mL/kg per hour). The infant's creatinine level is slightly elevated at birth, probably reflecting the mother's plasma concentration,¹⁷ and declines after birth. Thus, an increase in the serum creatinine level during the first days of life (based on multiple determinations rather than a single determination as studied here) may be more predictive of an elevated trough serum gentamicin concentration.

Decreased renal blood flow has been considered a side effect of high umbilical artery catheter placement and, thus, could have an effect on the clearance of gentamicin. This placement seemed to have minimal effect on gentamicin

clearance in our group of infants, however.

Infants receiving gentamicin therapy, especially preterm infants, frequently receive other drugs that potentially influence gentamicin pharmacokinetics or the clearance of gentamicin through an effect on renal function. Therefore, we reviewed the use of furosemide, dopamine, and indomethacin with gentamicin to determine their effects on trough serum gentamicin concentration.

Indomethacin, a prostaglandin synthetase inhibitor, is commonly used for the pharmacologic closure of a patent ductus arteriosus in the first days of life. Side effects associated with the use of indomethacin include hyponatremia, a 60% decrease in urine flow rate, a 30% to 40% decrease in glomerular filtration rate, and a variable decrease in electrolyte excretion and renal blood flow.¹⁸ Indomethacin has also been found to prolong the half-life of gentamicin through its effect on the glomerular filtration rate.¹⁸

Dopamine, a naturally occurring catecholamine, has a positive cardiac inotropic action and causes selective renal vasodilation in humans and animals.¹⁹ It has been used increasingly in recent years to treat low cardiac output and hypotension in premature infants. Dopamine also has been claimed to blunt the renal tubular side effects of indomethacin¹⁷ and, in low doses (2 to 7 μ g/kg per minute), increases renal blood flow.

Furosemide, a potent diuretic, promotes natriuresis and diuresis in premature infants. Its usage has been claimed to prevent the renal side effects of indomethacin.¹⁷

The use of these drugs with gentamicin could change the clearance of the antibiotic, either increasing it with the use of furosemide and dopamine or decreasing it with the use of indomethacin, and thus affect the measured serum concentration of gentamicin. However, no significant effect of these drugs on trough serum concentration was noted in our infants. The combination of the drugs received by some of the infants may have masked an effect of any one drug, but there were too few infants receiving more than one of the three drugs to test for this.

Our data confirm the association of trough serum concentration with dosing interval and birth weight. Similar associations have been found in other studies.^{1,4,6} This relationship appears to be independent of the other variables we studied.

We found that 58% of infants who weighed between 1000 and 1500 g had an elevated trough serum concentration on an 18-hour dosing schedule. We also noted a significant number of infants weighing between 2500 and 3250 g (Figure) who had an elevated trough serum concentration on the 12-hour dosing schedule. These results are somewhat different from those of Zarowitz et al,¹² who, in a prospective study, noted that on the third day of therapy, 21% of the infants between 28 and 34 weeks old on the 18-hour schedule and 41% of infants older than 34 weeks on a 12-hour schedule had trough serum concentrations higher than 2 mg/L.

To minimize the number of toxic trough serum concentrations while maintaining therapeutic peak concentrations, our data suggest the following modification of the dosing schedule during the first 4 days of life: for infants weighing 500 to 1500 g, a 24-hour dose interval, and for infants weighing 1500 to 2500 g, an 18-hour dose interval.

The most appropriate dose and interval for infants between 2500 and 3250 g is more problematic. We had 25 infants

in this group; 48% (12/25) had a toxic trough serum concentration and a therapeutic peak concentration. All of the 12 with an elevated trough concentration were on 12-hour dosing schedules, suggesting that this short dosing interval may not be optimal, even for these larger infants. Two of the remaining infants had a nontoxic trough concentration; however, their peak concentration was subtherapeutic. These two infants were on an 18-hour schedule; therefore, extending the interval may not be the satisfactory solution in these large infants. Wennberg and Goetzman¹⁹ recommend 3 mg/kg every 24 hours for infants weighing less than 2000 g and younger than 1 week. A dose of 3 mg/kg every 18 hours for newborns with birth weight between 2500 and 3250 g may provide a higher but nontoxic peak serum concentration, questionably more effective, and allow for a lower and less toxic trough concentration. However, we have not tested this hypothesis clinically.

Because so many infants receive prophylactic antibiotic therapy, it is important to minimize toxic effects; however, it is just as important not to treat infants inadequately if they have a life-threatening infection. The dose of 2.5 mg/kg every 12 hours seems to be satisfactory in term infants of greater than 3250-g birth weight, but may result in an unacceptably high number of toxic trough

serum concentrations in infants weighing between 2500 and 3250 g. Therefore, further studies are needed to determine optimal dosing in these infants. We have implemented the longer (24-hour) dosing interval to include infants weighing 1000 to 1500 g in our nursery and are collecting data to evaluate the prevalence of toxic trough or subtherapeutic peak concentrations on this protocol. Infants who weigh less than 1000 g continue to receive 24-hour dosing as previously described. The results of this study apply to newborns during their first days of life; infants who receive gentamicin beyond the first week of life may need a change in the dosing interval because of changing renal function during the first weeks of postnatal life. Indeed, a shorter dose interval (8 hours) has been recommended for term infants older than 7 days, based on this postnatal maturation of renal function. Our study did exclude infants who were still of very low birth weight at a postnatal age of older than 1 week. Further studies are needed to determine the changing pattern of gentamicin drug clearance in older preterm infants so that appropriate dose and dose-interval recommendations can be made.

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Morbidity and Mortality in Children With Pyogenic Liver Abscess

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• Review of our experience from 1975 to 1986 and a literature survey disclosed 109 children with pyogenic liver abscess. During this time, newer imaging techniques, especially ultrasonography and computed tomography, facilitated the prompt diagnosis of cystic lesions within the liver parenchyma. The incidence of pyogenic liver abscess at our institution (25 per 100 000 pediatric hospital admissions) was higher than previously reported. Since the majority of abscesses were located in the right lobe of the liver, patients were most effectively treated with percutaneous drainage of the abscess cavity. *Staphylococcus aureus* was the most common bacterial agent responsible for pyogenic liver abscess; however, anaerobic organisms were noted as a major group of pathogens and represented 27% of our patients. Furthermore, one patient was discovered to have multiple microabscesses of the liver associated with cat-scratch disease; pleomorphic gram-negative bacilli were not cultured. Among the 109 patients, the overall mortality of 15% was considerably better than that for children with PLA before 1975. The improved survival may be related to more prompt diagnosis of pyogenic liver abscess followed by evacuation of the liver abscess and antibiotic therapy.

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Pyogenic liver abscess (PLA) is a life-threatening disease in children that requires prompt diagnosis and therapy. Two extensive reviews in the pediatric literature are autopsy studies, which emphasize the high mortality for patients with this disorder.^{1,2} An incidence of 3 cases of PLA per 100 000 pediatric hospital admissions was reported³ for

years before 1977, with a mortality for these children of 36%. Recent reports in the adult literature describe a reduction in morbidity and mortality due to earlier diagnosis and improved therapeutic drainage procedures.^{4,5} Prompted by our experience involving three children with PLA during a 1-year period, we were interested in determining whether a similar reduction in morbidity and mortality could be determined for children.

PATIENTS AND METHODS

Eleven patients under 18 years of age were admitted to the University of Florida Shands Hospital, Gainesville, between January 1, 1975, and June 30, 1986, with the diagnosis of "liver abscess." Patients were included in this retrospective study if they met one or more of the following criteria: (1) percutaneous aspiration of purulent material from one or more intrahepatic cystic cavities, (2) demonstration of intrahepatic cavities by imaging techniques associated with positive blood cultures, and resolution of the symptoms after antimicrobial therapy, and (3) discovery of one or more liver abscesses at surgery or at autopsy.

Specific information was sought about initial symptoms, clinical signs, laboratory data including results of bacterial cultures, imaging techniques, open and closed PLA drainage procedures, antimicrobial therapy, and outcome. In addition, the number and location of liver abscesses and the presence of underlying diseases were noted.

RESULTS

The 11 patients with PLA identified since 1975 represented an incidence of approximately 25 per 100 000 hospital admissions (7 of these patients were previously described by Laurin and Kaude⁶ and 1 by Rizkallah et al⁷). There were 5 boys and 6 girls. The age at diagnosis ranged from 9 months to 17 years (mean, 7.5 years).

Clinical Data

The patients' symptoms and signs were nonspecific (Table 1). Abdominal pain was present in 10 (91%), fever in 9

(82%), and hepatomegaly in 8 (73%). The duration of the presenting symptom ranged from 1 to 90 days. Five patients presented with fever of unknown origin. The erythrocyte sedimentation rate was elevated (range, 32 to 122 mm/h; mean, 77 mm/h) in all 8 patients tested. Ten patients (91%) were anemic (hemoglobin level, 67 to 123 g/L; mean, 98 g/L) and 8 (73%) had leukocytosis (leukocyte count, 8.4 to 31.0 $\times 10^9$ /L; mean, 16.2 $\times 10^9$ /L). Alanine and aspartate aminotransferase levels were elevated in 3 patients (27%) (alanine aminotransferase levels, 112, 190, and 234 U/L; serum albumin level was low in 5 (45%) of 11 patients (27 to 33 g/L; mean, 30 g/L).

Five patients in our series had chronic granulomatous disease or leukemia that predisposed them to development of PLA. In two (patients 6 and 7), the underlying medical problems were unrelated to their liver abscess. Of the 11 patients, 4 had single and 7 had multiple abscess cavities. The abscesses were localized to the right lobe of the liver in 8 patients. *Staphylococcus aureus* was the organism most commonly isolated (Table 1). Anaerobes were cultured from the liver abscesses of 3 patients. One patient, with multiple small abscesses throughout the liver, had a positive cat-scratch skin test. His culture of liver tissue for bacterial and fungal agents was negative.

Diagnostic Findings

Ultrasonography, the most commonly employed imaging method, gave positive results in all eight patients studied. The lesions were hypoechoic in all but one patient, who had a mixed echo pattern. Usually the lesions were poorly delineated, although two patients (patients 4 and 10) had a rim of increased echogenicity around the abscess.

The technetium Tc 99m liver-spleen scan was positive in four patients, all with areas in the liver of reduced radio-

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The views expressed herein are those of the authors and not necessarily those of the United States Air Force or the Department of Defense.

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Table 1.—Clinical Data, Liver Abscess Culture, and Antibiotic Therapy in 11 Patients With Pyogenic Liver Abscess*

Patient/Age, y/Sex	Underlying Problems	Presenting Symptoms and Signs	Location and No. of Abscesses	Organisms	Antibiotics
1/2½/M	Chronic granulomatous disease	FUO, abdominal pain, hepatomegaly	R lobe, multiple	<i>Staphylococcus aureus</i> (liver)	Penicillin G potassium, gentamicin sulfate, methicillin sodium
2/14/F	None	FUO, abdominal pain, hepatomegaly	R lobe, multiple	<i>S aureus</i> (liver)	Methicillin, gentamicin
3/3/M	Chronic granulomatous disease	Fever, abdominal pain, hepatomegaly	R lobe, multiple	<i>S aureus</i> (liver)	Methicillin, metronidazole
4/13/M	Diabetes	R-sided chest pain, cough	R lobe, single	<i>Peptostreptococcus</i> (liver)	Penicillin
5/9½/F	Amebic liver abscess	Fever, vomiting, diarrhea, RUQ mass, hepatomegaly	R lobe, single	<i>Escherichia coli</i> (liver, peritoneal cavity)	Ampicillin, gentamicin, metronidazole
6/17/M	Sickle cell trait	Fever, abdominal pain	R lobe, single	<i>Peptostreptococcus</i> (liver)	Cefoxitin, penicillin
7/8/F	Recurrent UTI	FUO, abdominal pain, hepatomegaly	Both lobes, multiple	<i>Staphylococcus epidermidis</i> (liver)	Nafcillin sodium
8/2/F	None	Epigastric mass, abdominal distention	L lobe, single	<i>S aureus</i> (liver)	Nafcillin, cephalexin
9/3/M	Cat scratch disease	FUO, abdominal pain, hepatomegaly	Both lobes, multiple	None	Ampicillin, gentamicin, cefaclor
10/13/F	None	FUO, hepatomegaly, weight loss	R lobe, multiple	<i>S aureus</i> (liver)	Nafcillin
11/12/F	Perforated appendix, peritonitis	Fever, abdominal pain, vomiting	R lobe, multiple	<i>Bacteroides</i> , <i>Propionibacterium</i> (liver)	Penicillin, gentamicin

*FUO indicates fever of unknown origin; RUQ, right upper quadrant; and UTI, urinary tract infection.

activity. The gallium 67 scan performed in two children was normal. More recently, computed tomography (CT) of the liver was done in five children; the findings were abnormal in all cases, showing areas of reduced density within the liver. The CT scan provided the best definition of all three imaging modalities used. The diagnosis was confirmed by exploratory laparotomy and percutaneous aspiration of purulent material in six and five patients, respectively.

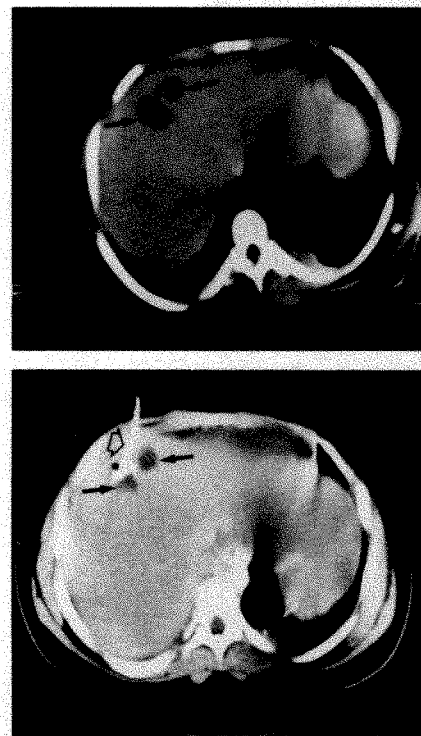
Treatment

In most patients, treatment consisted of the combination of a drainage procedure and appropriate broad-spectrum antibiotic therapy (Table 1). All patients were treated for 4 to 8 weeks with different combinations of parenteral and oral antibiotics. Six children (patients 1, 2, 5, and 7 through 9) had open drainage of their liver abscesses during laparotomy. The 1 patient (No. 5) with both PLA and amebic abscess was the only patient (1 of 11) who did not survive. Since 1980, four patients (Nos. 4, 6, 10, and 11) underwent successful percutaneous abscess drainage; fluoroscopic guidance was used for two of these patients. One (patient 3) did not require a drainage procedure. Recently, ultra-

sonography and CT scans have been the preferred methods of localization before the drainage procedure. The catheters were left in place for 2 to 3 weeks, until purulent material ceased to drain and the abscess cavity significantly decreased in size (Figure). Percutaneous drainage was effective in the four patients in whom it was attempted, and they all survived.

Previously Described Patients

During the same period of our experience, 98 children with PLA were described in the pediatric literature,⁸⁻⁴⁷ as catalogued by the National Library of Medicine. Together with our 11 patients, 67% were boys and 33% girls. Fifty-five percent of the 109 children were more than 5 years of age. Leukemia and chronic granulomatous disease were the most common predisposing conditions. The lesions were equally divided between single and multiple liver abscesses; they were localized to the right lobe of the liver in 73% of the patients. *Staphylococcus aureus* was the most commonly isolated organism. Enteric gram-negative bacteria accounted for 26 (31%) of 82 isolates, while anaerobes were recovered in 15% of the pa-



Upper-abdominal computed tomographic scans in patient 11 after contrast enhancement. Top, Two low-density oval lesions in the right lobe of the liver (black arrows). Bottom, Scan of the same patient after placement of percutaneous drainage catheter (open arrow).

tients. Excluding a large autopsy study of neonates,² infant and child mortality was 15%.

Diagnostic imaging techniques included radioisotope scanning, ultrasonography, CT scans, and angiography (Table 2). Overall, they were all sensitive investigations, especially the angiography, but it was done in only 9 of the 109 patients. The CT scans failed to identify the lesion in only 1 patient with multiple microabscesses. Neither ultrasonography nor radioisotope scanning proved to be as sensitive as CT scans, giving false-negative results in 12 (21%) of 58 and 8 (19%) of 43 patients, respectively. For the radioisotopic scans, gallium 67 failed to yield a diagnosis in 5 (38%) of 13 patients, and the technetium Tc 99m scan was falsely negative in 4 (9%) of 45. The diagnosis of liver abscess was confirmed by laparotomy in 56% of patients, by percutaneous aspiration in 24%, and at autopsy in 20%.

Laparotomy with open drainage was the procedure most commonly performed (Table 3). It was done in 46 patients, with a mortality of 11%. Percutaneous drainage of the liver abscess was accomplished in 11 patients, all of whom survived. In one patient, the percutaneous procedure was unsuccessful, necessitating open drainage to evacuate the abscess adequately.⁴⁵ Failure to drain the purulent material was accompanied by a high mortality: 20 (47%) of 43 patients died. In 17 of 20 patients who died without a drainage procedure, the diag-

nosis was made at autopsy. The majority of the 23 survivors in this latter group had multiple microabscesses that were treated with antimicrobial agents.

COMMENT

Review of our experience from 1975 to 1986 and a literature survey since 1977 revealed 109 well-documented cases of PLA in patients less than 18 years of age, compared with 61 children described between 1935 and 1977.³ This higher incidence of PLA in children during the past decade compares more closely with rates noted for adults with this disease.^{4,5} For adults and children, the incidence may be due, in part, to the improved imaging techniques available to diagnose PLA in some patients in whom it was previously unrecognized. Another reason may be the improved survival of patients with chronic granulomatous disease and leukemia who are at risk for developing liver abscesses. The prolonged lifespan of patients with primary and secondary immune defects could also account for older children with PLA since 1977. Approximately 50% of the 109 patients were more than 6 years of age, in contrast to reports before 1977, in which 66% of the patients were less than 5 years old.^{1,3}

In the last decade, newer imaging techniques have made for earlier diagnosis of PLA in children, who usually have a nonspecific clinical presentation. Angiography, an invasive procedure that may yield nonspecific findings, is almost never necessary to diagnose PLA in children. The CT scans of the liver provided the best sensitivity and specificity of all imaging techniques for our patients and those described in recent studies. Detailed images can be obtained due to its high resolution.⁴⁶ Ultrasonography and radioisotope scans are, overall, not as sensitive. However, among our 11 patients, the liver ultrasound scan was positive in all 8 patients studied.

Once a cystic mass is identified in the liver, diagnostic considerations other than pyogenic abscess include congenital cyst, arteriovenous malformation, hepatic tumor with central necrosis or hemorrhage, and amebic abscess. This last diagnosis is the most important differential diagnostic consideration. In many parts of the world, amebic abscess is a far more frequent diagnosis than

PLA. In addition to ethnicity, patients with amebic abscess are more likely to have abdominal pain and a history of diarrhea, but the signs and symptoms often mimic those of PLA. Abdominal CT scan is the best method of detecting amebic liver abscess and its extrahepatic abnormalities, such as pleural effusion and amebic colonic involvement. Most importantly, the presence of an elevated amebic antibody titer in the setting of a hepatic abscess is diagnostic of amebic abscess.

In the appropriate clinical setting, the diagnosis of PLA must be confirmed by aspiration of purulent material from the suspected abscess cavity. A percutaneous aspiration with ultrasound or CT guidance can be accomplished if the size and location of the abscess make it feasible.⁴⁶ Since 75% of the abscesses are located in the right lobe of the liver, a percutaneous aspiration can be considered in the majority of children.

The choice of antibiotics is determined by the results of the culture and corresponding sensitivity studies. *Staphylococcus aureus* remains the single most common cause of PLA. Enteric gram-negative organisms taken as a group are as frequent as *S aureus*. Anaerobes, identified in 27% of children in our small series and 15% of the 109 patients, are a third major group of pathogens. For children, this is in contrast to the rare report before 1977 of hepatic abscess due to anaerobic bacteria—probably a direct result of improved diagnostic culture techniques since that time.^{4,5} Although pleomorphic gram-negative bacilli were not cultured from any tissue of our patients, one child (patient 9) had a positive cat-scratch test after a well-documented scratch by an animal before the development of acute disease. Liver abscesses complicating cat-scratch disease should be considered even in the absence of abnormal results of liver function tests.⁷

Furthermore, if the abscess is located in the right lobe of the liver and has a well-defined cavity, drainage by percutaneous catheter should be attempted.⁵⁰ Adult patients with PLA have been successfully treated by repeated needle aspiration.⁵¹ The first continuous closed drainage in a patient with PLA was performed many years later.⁵² Recently, adults and children were treated by percutaneous drainage or aspiration of the

Table 2.—Diagnostic Imaging Findings in 109 Children With Liver Abscesses

	No. Positive/ No. Tested	% Positive
Radioisotope scan	46/58	79
Ultrasonography	35/43	81
Computed tomography	24/25	96
Angiography	9/9	100

Table 3.—Drainage Procedures and Mortality in Treatment of Pyogenic Liver Abscesses

Drainage Procedure	No. of Deaths/ No. of Patients	Mortality, %
Open drainage	5/46	11
Percutaneous drainage	0/11	0
None	20/43	47
Total	25/109*	23

*Insufficient information on 9 of 109.

abscess cavity^{30,53}; in one study, the procedure was effective in 58 patients and the mortality was 1.5%.³⁰ While pediatric experience is limited, the recent adult literature suggests that percutaneous drainage should be the initial therapy for patients with PLA.^{54,55} However, despite a well-documented record of efficacy, reasons for the limited use of closed drainage procedures in adults are unclear. This may, in part, be related to the role of percutaneous drainage in patients with multiple large PLAs, in whom the mortality from PLA is at least doubled.⁵⁶ Specific disadvantages include complications and failure of the procedure due to technical problems and occasionally a prolonged hospital admission when compared with medical or surgical treatment alone.^{54,57}

In summary, PLA should be suspected in any child with unexplained, persistent fever; abdominal pain; and hepatomegaly. If a cystic cavity is found within the liver parenchyma by ultrasonography or CT scan, aspiration of the lesion should be considered to confirm the diagnosis. In the majority of patients it is usually feasible to attempt percutaneous drainage initially, except in those patients with multiple microabscesses or left-lobe abscesses. The more recent improved outcome for children with PLA may be secondary to earlier diagnosis with prompt drainage of the abscess and precise antibiotic therapy. Careful attention should always be given to the isolation of anaerobic organisms from the cystic cavity of the liver. Amebic liver abscess is another important diagnosis to exclude with hemagglutination/complement fixation tests. A skin test with cat-scratch antigen is also necessary, especially for those children with multiple microabscesses.

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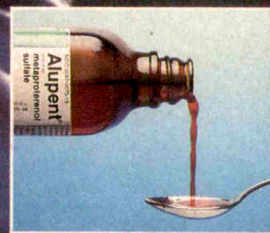


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Brief Summary of Prescribing Information

CONTRAINDICATIONS Use in patients with cardiac arrhythmias associated with tachycardia is contraindicated.

Although rare, immediate hypersensitivity reactions can occur. Therefore, Alupent® (metaproterenol sulfate USP) is contraindicated in patients with a history of hypersensitivity to any of its components.

WARNINGS Excessive use of adrenergic aerosols is potentially dangerous. Fatalities have been reported following excessive use of Alupent® (metoprolol sulfate USP) as with other sympathomimetic inhalation preparations, and the exact cause is unknown. Cardiac arrest was noted in several cases.

Alupent, like other beta adrenergic agonists, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or ECG changes. As with other beta adrenergic aerosols, Alupent can produce paradoxical bronchospasm (which can be life threatening). If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

Alupent® (metaproterenol sulfate USP) should not be used more often than prescribed. Patients should be advised to contact their physician in the event that they do not respond to their usual dose of a sympathomimetic amine aerosol.

PRECAUTIONS General: Extreme care must be exercised with respect to the administration of additional sympathomimetic agents.

Since metaproterenol is a sympathomimetic amine, it should be used with caution in patients with cardiovascular disorders, including ischemic heart disease, hypertension or cardiac arrhythmias, in patients with hyperthyroidism or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines or who have convulsive disorders. Significant changes in systolic and diastolic blood pressure could be expected to occur in some patients after use of any beta adrenergic bronchodilator.

Information for Patients: Extreme care must be exercised with respect to the administration of additional sympathomimetic agents. A sufficient interval of time should elapse prior to administration of another sympathomimetic agent.

Drug Interactions: Other beta adrenergic aerosol bronchodilators should not be used concomitantly with Alupent because they may have additive effects. Beta adrenergic agonists should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of beta adrenergic agonists on the vascular system may be potentiated.

Carcinogenesis/Mutagenesis/Impairment of Fertility: In an 18-month study in mice, Allupent produced an increase in benign ovarian tumors in females at doses corresponding to 320 and 640 times the maximum recommended dose (based on a 50 kg individual). In a two-year study in rats, a non-significant incidence of benign leiomyomata of the mesovarium was noted at 640 times the maximum recommended dose. The relevance of these findings to man is not known. Mutagenic studies with Allupent have not been conducted. Reproduction studies in rats revealed no evidence of impaired fertility.

Pregnancy *Teratogenic Effects: Pregnancy Category C:* Alupent® (metaproterenol sulfate USP) has been shown to be teratogenic and embryotoxic in rabbits when given orally in doses 620 times the human inhalation dose and 62 times the human oral dose. There are no adequate and well-controlled studies in pregnant women. Alupent should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Oral reproduction studies in mice, rats and rabbits showed no teratogenic or embryocidal effects at 50 mg/kg, corresponding to 310 times the human inhalation dose and 31 times the human oral dose. Teratogenic effects in the rabbit included skeletal abnormalities and hydrocephalus with bone separation on

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Alupent* (metaproterenol sulfate USP) is administered to a nursing woman.

Pediatric Use Consult package insert for age limit

ADVERSE REACTIONS Adverse reactions are similar to those noted with other sympathomimetic agents. Adverse reactions such as tachycardia, hypertension, palpitations, nervousness, tremor, nausea and vomiting have been reported.

The most frequent adverse reaction to Alupent® (metaproterenol sulfate USP) administered by metered-dose inhaler among 251 patients in 90-day controlled clinical trials was nervousness. This was reported in 6.8% of patients. Less frequent adverse experiences, occurring in 1-4% of patients were headache, dizziness, palpitations, gastrointestinal distress, tremor, throat irritation, nausea, vomiting, cough and asthma exacerbation. Tachycardia occurred in less than 1% of patients.

HOW SUPPLIED *Inhalation Aerosol:* Each Alupent® Inhalation Aerosol contains 150 mg of metaproterenol sulfate as a micronized powder in inert propellants. Each metered dose delivers through the mouthpiece 0.65 mg. metaproterenol sulfate (each mL contains 15 mg). Alupent Inhalation Aerosol with Mouthpiece (NDC 0597-0070-17), net contents 14g (10mL), equipped with blue protective cap. Alupent Inhalation Aerosol Refill (NDC 0597-0070-18), net contents 14g (10 mL).

Store between 59°F (15°C) and 77°F (25°C). Avoid excessive humidity.

Inhalation Solution: Alupent Inhalation Solution is supplied as a 5% solution in bottles of 10 mL or 30 mL with accompanying calibrated dropper. Store below 77°F (25°C). Protect from light. Do not use the solution if it is brown or has a precipitate.

Alupent Inhalation Solution Unit-dose Vial is supplied as a 0.4% or 0.6% clear colorless or nearly colorless solution containing 2.5 mL, with 25 vials per box. Store below 77°F (25°C). Protect from light. Do not use the solution if it is brown or has a precipitate.

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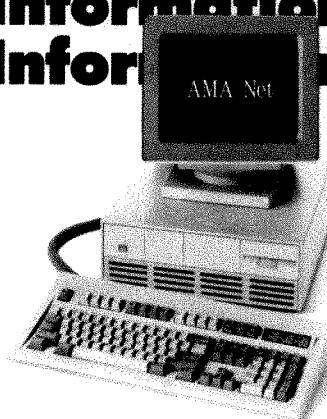
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Fetal Surgery in the 1990s

Mark I. Evans, MD; Arie Drugan, MD; Frank A. Manning, MD; Michael R. Harrison, MD

In the recent past, the first opportunity to visualize fetal structure and function occurred at birth. Two major contributions in the 1960s inaugurated the era of the *fetus* as a patient: (1) Prenatal diagnosis became possible using amniocentesis as a technique to evaluate fetal health by cytogenetic¹ and biochemical^{2,3} analysis. (2) Prenatal treatment became possible using fetal transfusion to control rhesus factor erythroblastosis fetalis.⁴ Intrauterine exchange transfusions through an open abdomen and uterine incision were attempted and abandoned due to unacceptably high maternal morbidity associated with "open" procedures.⁵ The development of less invasive techniques for percutaneous placement of catheters or needles for intraperitoneal transfusion permitted in utero exchange transfusion.⁶

In the 1970s, the introduction of fetal ultrasonography allowed for accurate visualization of the structure and function of the fetus.⁷ As skill and technology advanced, the list of fetal anomalies able to be diagnosed by ultrasonography expanded.⁸ Maternal serum α -fetoprotein screening⁹ has increased the ability to detect some anomalies that might not otherwise have been detected. The combination of ultrasonography with maternal serum α -fetoprotein

screening⁹ allows for prenatal diagnosis of anomalies of the fetal neural tube, abdominal wall, urinary system, or the lymphatic system (ie, cystic hygroma). After the diagnosis of a fetal anomaly prior to 24 weeks' gestation, parents have a choice between termination of pregnancy or preparing for the birth of an "affected child." It is our belief that parents should be told of the option of abortion; no matter how serious the anomaly, the option must always be presented to the parents when legally permissible. If the pregnancy is continued, knowledge of the defect has potential psychological advantages for the parents and definite logistic advantages for the pediatric staff who will care for the infant after birth.

In a very limited number of circumstances, there may be another option, ie, treatment before birth. Both surgical and medical approaches have been attempted. We will review the status of surgical interventions. Other reviewers have dealt with the cardiac¹⁰ and biochemical¹¹ aspects of medical fetal therapy and the potential for gene therapy.¹²

When a potentially correctable fetal anomaly is diagnosed, the following factors must be considered:

1. What is the natural outcome of this anomaly? Will additional or irreversible damage be caused to the fetus if repair procedures are delayed until after birth?

2. Is it possible to correct the anomaly or its consequences in utero? Will the procedure change the natural outcome?

3. What is the risk to the mother and the fetus?

Surgical intervention in utero should be considered only if the natural history of the anomaly is associated frequently with neonatal severe handicap or early death, if there is evidence (from animal

models) that the natural history of the anomaly can be altered by the surgical procedure, and if the risk to the mother is relatively small as proved in a rigorous animal model (eg, the nonhuman primate).

In the early 1980s, investigators identified several fetal diseases in which a simple anatomic defect interferes with organ development and might be amenable to correction: hydronephrosis, hydrocephalus, and diaphragmatic hernia.^{13,14} The International Fetal Medicine and Surgery Society began meeting in 1982 and formulated guidelines for fetal intervention.¹⁵ They also established a registry to record all cases of obstructive uropathy and obstructive ventriculomegaly in which in utero operative procedures were undertaken. Registries for fetal medical treatment, cardiac arrhythmias, chylothorax, etc, have since been established, and reports are published periodically.¹⁶

FETAL VENTRICULOMEGALY

In the early 1980s, much of the focus of the potential for fetal therapy centered on obstructive ventriculomegaly. Interest in this disorder emerged from the relative ease to diagnose such anomalies by then-available ultrasound technology and was amplified by the success rates of shunting procedures performed in the neonate.¹⁷ The concept, as developed in animal models, was that early shunting of ventriculomegaly in utero might prevent the irreversible damage caused by prolonged increased intracranial pressure.¹⁸⁻²⁰ In humans, however, the results of ventriculoamniotic shunts were very disappointing. As of July 1, 1989, 45 cases of fetal ventriculomegaly treated in utero by long-term ventriculoamniotic shunts were reported to the International Fetal Registry (Table 1).¹⁶

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In the majority of instances, the shunting was performed for a fetus presumed to have ventriculomegaly-hydrocephalus secondary to aqueductal stenosis. The mean (\pm SD) gestational age at diagnosis was 25 ± 2.73 weeks (range, 18 to 31 weeks), and the mean age at treatment was 27 ± 2.6 weeks (range, 23 to 33 weeks). The duration of effective therapy cannot be determined from Registry data since objective means of assessment of shunt function are not available. Thirty-four (83%) of 41 fetuses with hydrocephalus treated by ventricular amniotic shunting have survived. Of the 7 deaths that occurred, 4 could be directly attributed to trauma at the time of placement of the shunt or to premature labor occurring within 48 hours of shunt placement. The crude mortality rate for the procedure is, therefore, 9%. The 38 surviving infants have been followed up on average for 12.2 ± 5.8 months (range, 6 to 36 months). Fourteen (35.3%) of the 34 surviving fetuses, all with aqueductal stenosis, are reported as "normal" at follow-up (Table 2). The remaining 24 survivors have all exhibited varying degrees of neurological handicap, the majority of whom (18 [53%] of 34 survivors) are classified as having severe handicaps. These infants all exhibited gross delay in reaching developmental milestones, and the tested developmental quotient was always less than 60. Five of these infants have had cortical blindness, 3 have had seizure disorders, and 2 have spastic diplegia. Outcome among survivors was principally related to the primary cause of obstructive hydrocephalus. Aqueductal stenosis of uncertain origin was the most common causative factor for obstructive hydrocephalus (28 [68%] of 41 cases), and the only intact survivors were found in this group.

The results of ventriculoamniotic shunting for fetal ventriculomegaly, therefore, have been quite disappointing, and there are no one-way valve shunt devices available even if one wanted to treat a patient; thus, there is a "de facto" moratorium in place.^{21,22} The hope, which was to take fetuses that would otherwise be severely impaired by ventriculomegaly and to avoid irreversible damage by intrauterine treatment, was substituted in a few unfortunate instances, with survival of se-

Primary Diagnosis (Postnatal)	No. of (% of Total) Cases	No. of Deaths	Mortality by Diagnosis, %	No. of Survivors	Survival by Diagnosis, %
Aqueductal stenosis	32 (76.9)	4	13.3	28	87.5
Associated anomalies	5 (12.7)	2	40	3	60
Holoprosencephaly	1 (2.6)	1	100	0	0
Dandy-Walker syndrome	1 (2.6)	0	0	1	100
Porencephalic cyst	1 (2.6)	0	0	1	100
Arnold-Chiari syndrome	1 (2.6)	0	0	1	100
Total	41 (100)	7	17	34	83

Primary Diagnosis (Postnatal)	No. of Survivors	Outcome, No. (%) of Patients		
		Normal	Mild/Moderate Handicap	Severe Handicap
Aqueductal stenosis	28	12 (42.8)	2 (7.2)	14 (50)
Associated anomalies	3	0 (0)	0 (0)	3 (100)
Dandy-Walker syndrome	1	0 (0)	1 (100)	0 (0)
Porencephalic cyst	1	0 (0)	0 (0)	1 (100)
Arnold-Chiari syndrome	1	0 (0)	1 (100)	0 (0)
Total	34	12 (35.3)	4 (11.8)	18 (52.9)

verely affected infants who would have otherwise mercifully died.

Despite the seemingly poor outcomes in treated fetuses, abandonment of the concept of shunting for ventriculomegaly must be reconsidered for several reasons. Analysis of the cases of ventriculoamniotic shunt placement performed in the 1980s reported in the Registry shows that selection criteria were not always employed appropriately, and fetuses with ventriculomegaly associated with other severe anomalies (ie, holoprosencephaly or autosomal trisomies) were also, in many instances, given the "benefit" of intrauterine treatment.

Current reports have also demonstrated that the natural history of fetal ventriculomegaly is also quite dismal.^{23,24} The major determinant of prognosis was the association with other intracranial or extracranial malformations. Additional malformations affect

70% to 85% of fetuses with ventriculomegaly, and all such cases end in perinatal mortality or severe morbidity. Moreover, even if a diligent search for additional malformations is performed, combining a detailed ultrasound study of the fetus with amniocentesis for karyotype and amniotic fluid α -fetoprotein and acetylcholinesterase, 20% to 40% of abnormalities will not be detected even by experienced personnel.^{23,24} The obvious candidates for in utero ventricular shunt—the fetuses with isolated progressive ventriculomegaly—are limited in number by a high rate of associated anomalies and by the relative failure to exclude additional malformations prenatally. Moreover, the severity of ventriculomegaly is not always predictive of outcome or even of the need for postnatal shunt, as ventriculomegaly may not be associated with elevated intracranial pressure.

Considering the uncertainties of benefit and risk and the difficulties of accurate prenatal diagnosis, intrauterine treatment of fetal ventriculomegaly remains a controversial and highly experimental procedure. However, when the option in midtrimester is between termination of pregnancy or inactive observation of progressive dilatation of the ventricles, placement of a ventriculoamniotic shunt should present a third option to be considered in very selected cases.²² Given the small numbers of "good" candidates and the need to develop a new catheter (as none is currently available), a new study would be best performed in only one or two centers in North America experienced in the technical aspects of ventriculoamniotic shunt placement. Obviously, this experience is now lacking when there exists a de facto moratorium on intrauterine treatment of ventriculomegaly. It is hoped that there can now be a reconsideration and study of ventriculomegaly shunting that may answer the question of its usefulness for the limited number of appropriate patients.²⁴

OBSTRUCTIVE UROPATHY IN THE FETUS

The widespread use of obstetric ultrasonography and the increase in resolution and technical expertise allow the recognition of obstructive uropathy more frequently and earlier in pregnancy.^{24,25} Retrograde pressure forms behind the obstruction and causes increasing dilatation of the urinary system. As documented in animal studies, hydronephrotic and, perhaps, dysplastic changes occur in the renal parenchyma.²⁶⁻²⁹ The severe oligohydramnios associated with bilateral urinary tract obstruction results in pressure deformities of the face and limbs and pulmonary hypoplasia; neonatal death is caused by respiratory insufficiency. The timing and the degree of obstruction are crucial determinants in the development of irreversible renal and pulmonary damage.^{30,31}

Intrauterine treatment should be reserved for patients with bilateral urinary tract obstruction, maintained renal function, decreased amniotic fluid volume, and no other life-threatening anomalies. Cytogenetic anomalies and congenital malformations of other systems are diagnosed in 15% to 40% of

cases of fetal obstructive uropathy.^{32,33} The evaluation should include the karyotype (by amniocentesis, transabdominal chorionic villus sampling, or cordocentesis), echocardiography, and a detailed ultrasound examination to assess renal size or dysplastic changes, to evaluate fetal bladder filling, and to exclude additional malformations. If fetal visualization is hampered by severe oligohydramnios, artificial instillation of fluid will improve sonographic visibility and the observation of fetal behavior (drinking, filling of stomach and bladder), allowing more accurate study of the fetal anatomy.³⁴

The evaluation of fetal renal function is based on ultrasonographic observation of bladder filling (after urine aspiration), absence of renal cortical cysts, and analysis of urine osmolality and electrolytes.³⁵ None of these tests are, however, infallible. The bladder may fill from secretion by bladder mucosa. The ultrasonic demonstration of renal cortical cysts has a specificity of 100% and a sensitivity of 44% in identifying renal dysplasia with irreversible damage.³⁶ Hypotonic fetal urine (sodium, <100 mmol/mL; chlorine, 90 mmol/mL; osmolality, <210 mmol/L) suggests maintained glomerular and tubular function. However, while abnormal electrolyte levels and osmolality in fetal urine are associated with poor prognosis in the vast majority of cases, hypotonic urine does not reliably exclude the finding of dysplasia or neonatal evidence of severe renal dysfunction.^{31,37} Urinary electrolytes normally drop with gestational age (C. Rodeck, MD, oral communication, July 8, 1989).

Dumez et al³⁸ have evaluated multiple urinary variables and found β_2 -microglobulin, ammonia, and creatinine, to be good predictors of renal function and long-term outcome. Overall, the best ultrasonic indicator of the severity of the disease appears to be the decrease in amniotic fluid volume. When the fetus develops severe oligohydramnios before the 20th week of gestation, the prognosis is most commonly dismal.³⁵

Most procedures of vesicoamniotic shunt placement have been performed percutaneously under ultrasonographic guidance. A double-coiled nylon catheter was used in most cases with good results. Unlike brain shunts, one-way

valve catheters are not necessary since the pressure in the obstructed bladder almost always exceeds that in the amniotic fluid.

The function of these shunts may, however, be impaired by occlusion or displacement, necessitating close observation and replacement of the non-functioning shunt. When weeks to months of continuous drainage are required, some favor open surgical decompression by bladder marsupialization or bilateral ureterostomies.^{35,39-41} This would involve, however, an increased risk for both mother and fetus. Of the 87 cases of fetal obstructive uropathy reported to the Registry as of July 1, 1989, there have been 35 survivors (40.2%) (Table 3). The oldest survivor is now 7 years of age and appears to be developing normally. The mean (\pm SD) gestational age at initial referral has been 23 ± 4.6 weeks (range, 14 to 34 weeks). The mean age at in utero therapy has been 24.2 ± 5 weeks (range, 14 to 36 weeks). No uniformity in shunt design, construction material, or method of shunt placement is recorded. Of the 87 cases, 13 (14.9%) were electively terminated after shunt placement. In 7 of these instances, termination was elected because of abnormal karyotype, and in 6 instances because of a suspected or proved major renal dysfunction. Of the remaining 74 ongoing pregnancies, there have been 35 fetal survivors (47.3%). Perinatal survival is strongly related to the primary cause of obstructive uropathy, and the criteria for diagnosing the cause of the disease have continued to improve. The best survival is reported among fetuses with proved posterior urethral valve syndrome (68%).

The long-term follow-up data of these children are now becoming available. To date, chronic morbidity is being reported in only 3 (8.6%) of 35 survivors. One of these children with post-urethral valve syndrome has developed chronic renal failure requiring hemodialysis. One survivor has borderline renal function and chronic pulmonary insufficiency that is progressed at 2 years of age. A third female child has required extensive and ongoing corrective surgery for a persistent cloacal syndrome. The operative mortality rate remains relatively constant. The death rate directly at-

Table 3.—Fetal Obstructive Uropathy: Primary Diagnosis and Outcome in 87 Treated Cases*

Primary Diagnosis	No. of (% of Total) Cases	No. of Survivors	Survival by Diagnosis, %
Posterior urethral valve syndrome	25 (28.7)	17	68
Karyotype abnormality†	7 (8)	0	0
Renal dysplasia noted by ultrasound†	6 (6.9)	0	0
Urethral atresia	6 (6.9)	1	20
Prune-belly syndrome	5 (5.7)	4	16.7
Unknown	1 (1.1)	1	100
Ureteropelvic obstruction	2 (2.3)	2	100
Unknown origin	35 (40.2)	10	28.6
Total	87 (100)	35	40.2

*Primary diagnosis was confirmed by antenatal or neonatal assessment or by autopsy.

†In these cases, pregnancy was electively terminated.

tributable to vesicoamniotic shunting has been 4.7% (4/85 cases).

These data may be interpreted to suggest that there is a defined role for chronic vesicoamniotic shunting in fetuses with bilateral hydronephrosis secondary to urethral obstruction (usually male patients with posterior urethral valves). To be appropriate candidates, fetuses must (1) have normal karyotypes and have progressive and persistent disease, (2) have time to develop pulmonary tissue, (3) have good prognostic criteria (good fetal urine electrolytes and osmolality), and (4) have normal renal parenchymal echogenicity without cysts at the time of preoperative assessment.

It is apparent in reviewing the recent data referred to the Registry¹⁶ that much more selective criteria are being used now before a patient is considered a candidate for fetal surgery. Most notably, use of fetal urinary electrolyte levels and osmolality have had a major discriminating effect. As a result, survival in treated fetuses is continuing to improve, whereas the proportion of evaluated fetuses being treated continues to fall.

OPEN FETAL SURGERY

While the percutaneous approach under ultrasonographic guidance seems to be the preferred method for placing a shunt in a hollow enlarged viscus, the correction of more extensive fetal anomalies will require more extensive and more invasive surgery on both

mother and fetus. The feasibility of open fetal surgery was anecdotally demonstrated in the 1960s when an open technique was used for intrauterine exchange transfusions in erythroblastosis fetalis.⁴² However, preterm labor and abortion made this initial experience so discouraging that direct exposure of the fetus was abandoned for over a decade. In the late 1970s and early 1980s, interest in open fetal surgery was revived by two factors. Prenatal diagnosis of some simple anatomic defects with disastrous consequences for the developing fetus (eg, fatal pulmonary hypoplasia secondary to urinary tract obstruction or diaphragmatic hernia) was being recognized. At the same time, neonatologists and pediatric surgeons were coming to grips with the futility of attempting to salvage these infants after birth. It is most important to note that the outcome of some prenatally detected conditions such as diaphragmatic hernia is markedly different from that of the "same" postnatally detected lesion. While the survival of postnatally detected diaphragmatic hernia is high, the prenatally detected condition is worse and has at best a 20% survival.⁴³⁻⁴⁵

It became apparent that the only way to salvage fetuses with these lesions was open surgery. However, the open approach could be justified only if the following criteria were met:

1. The natural history of the human fetal disorder is defined and selection of only those fetuses with the disorder who are likely to benefit from intervention is possible.

2. The pathophysiologic structure of the disorder and the efficacy of in utero correction were established in animal models.

3. The proposed procedure was proved feasible and safe for both fetus and mother in a rigorous, nonhuman primate model. Extensive experience with fetal surgery in sheep and phylogenetically lower animals could not be used to evaluate the feasibility and safety of fetal intervention in humans because the biological gestation is dissimilar and hysterotomy seldom induces preterm labor and abortion. The primate uterus, on the other hand, is exquisitely sensitive to surgical manipulation, making success in this model a rigorous criteria for human application.

In the early 1980s, a group in San Francisco, Calif, satisfied these criteria by studying the pathophysiologic structure of diaphragmatic hernia⁴⁶⁻⁴⁸ and hydronephrosis²⁶⁻³⁰ in animals, by defining the natural history and outcome of diaphragmatic hernia⁴³⁻⁴⁵ and obstructive uropathy^{35,39-41} in human fetuses, and by developing the anesthetic, pharmacologic, and surgical techniques in the nonhuman primate necessary to make open fetal surgery safe for both mother and fetus.⁴⁹⁻⁵¹ The techniques developed in the laboratory have been applied to 12 highly selected human cases (5 uropathies,⁵² 6 diaphragmatic hernias,⁵³ 1 sacrococcygeal teratoma⁵⁴) by Harrison et al since 1982. Four procedures were technically unsuccessful and a fetectomy was performed; in the other 6, the fetus survived and was eventually delivered by a second cesarean section. The details of these initial cases have been reported.⁵²⁻⁵⁴ The most important aspect in this initial phase 1 trial of open fetal surgery was maternal safety. There were no significant intraoperative complications. Operative blood loss ranged from 200 to 1000 mL, but none of the patients required transfusion. There were no wound infections or complications, and hospital stay following fetal surgery varied from 5 to 13 days (mean, 7.7 days). Two patients developed amniotic fluid leaks postoperatively that were due to the technique of uterine closure, which has since been corrected. The most common postoperative problem was uterine irritability, and all patients required tocolytic therapy. Pre-

mature labor remains a constant threat and is the major morbidity associated with fetal surgery. Four of these patients have had subsequent normal pregnancies, suggesting that fetal surgery does not interfere with reproductive capacity. Of these initial cases, all of the patients with uropathy have survived with variable renal function. Of the initial patients with diaphragmatic hernias, the first three were technically unsatisfactory. The last was delivered at 31 weeks, and the infant did well for several weeks. At 5 weeks post partum, a second operation was performed to remove the abdominal patch. Unfortunately, 2 days later, following an intubation accident, the infant died. Three of these patients have had subsequent normal pregnancies, suggesting that fetal surgery does not interfere with reproductive capacity.

These first cases of open fetal surgery represent a steep learning curve, but the overall experience argues for continued cautious application of these surgical procedures. Open fetal surgery is technically difficult but feasible, and thus far it has proved safe for mother and her reproductive potential. The efficacy of these procedures in reversing potentially fatal fetal maldevelopment remains to be proved.

FETAL SURGERY: AN OVERVIEW

Improvement in ultrasound technology and increased use of maternal serum α -fetoprotein screening in the last decade have resulted in the prenatal diagnosis of many disorders for which prenatal treatment could improve outcome. The experience with ultrasound-guided, percutaneous procedures developed for the treatment of erythroblastosis fetalis has proved this method to be safe for both fetus and mother. The success of the less-invasive shunt techniques has contributed to the shift of

interest away from more-invasive open fetal surgery.⁵⁵ It is clear, however, that the correction in utero of lesions that are more complex in nature, such as congenital heart lesions, diaphragmatic hernia, or meningomyelocele, will necessitate open forms of surgery.^{55,56} Although open fetal surgery appears to be relatively safe in terms of pregnancy loss or uterine rupture in pregnancy, it still involves the mother in two major surgical procedures within a relatively short period—one for fetal treatment and the other for cesarean delivery. The morbidity and mortality associated with major surgery during pregnancy are considerable.⁵⁷ Presently, state-of-the-art open fetal surgery is still a highly experimental procedure. Fetal surgery represents a formidable undertaking whose short- and long-term risks and benefits need to be documented and studied. Studies should continue on animal models aiming to improve the technical aspects and increase fetal and maternal safety of open fetal surgery; demonstrated success in the nonhuman primate model should be a requisite for any center to attempt open fetal surgery in humans. The initial cautious attempts to correct a few carefully selected lesions (diaphragmatic hernia, sacrococcygeal teratoma, severe uropathy) should continue only in those few centers dedicated to developing this experimental technique. As with other procedures of highly experimental nature, the need for institutional review board review, a detailed informed consent, honest and pragmatic parental counseling, and meticulous documentation and follow-up of every case cannot be overemphasized.

Percutaneous placement of amniotic shunts seems to be relatively safe, thereby shifting the risk ratio in favor of these procedures. Problems of accurate diagnosis and patient selection do, however, affect the success rate and ulti-

mate outcome. Fetuses affected by posterior urethral valves and isolated ventriculomegaly have the best chances of intact survival. Although excluding all associated anomalies is difficult and sometimes impossible, the minimal requirements before counseling intrauterine fetal therapy should include a satisfactory level III ultrasound, echocardiography, and fetal karyotype. A functional evaluation of the organ involved is also important. While urinalysis, rate of bladder filling, and ultrasonographic appearance of the kidneys may give an indication of whether fetal renal function is already irreversibly damaged, more subtle tests are needed to prove that fetal renal function is maintained. Likewise, the degree of ventricular dilatation, the cerebral mantle width, or even the progression of the process do not seem to correlate well with the need for shunt placement after birth or with subsequent intelligence.²³ Functional assessment of in utero intracranial disease may be possible; visual evoked potential in the fetal lamb appear to correlate with hypoxia, intracranial pressure, and hydrocephaly.⁵⁸

The problems of patient selection and diagnostic accuracy need to be solved during the coming years. While the answer to the "on whom to operate" question seems clear, an educated decision on which fetus to operate (and, more importantly, on which fetus *not* to operate) in utero is expected to result from the cumulative experience with fetal surgery during the next years. During this formative period for fetal surgery, it is vitally important that every case of fetal surgery is reported in detail to the Registry. Intrauterine fetal surgery is here to stay. Its future depends on cooperation and team approach. If properly applied, fetal surgery could improve the length and quality of life of some fetuses that otherwise would have lost the race even before reaching the starting line.

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Clinical Predictors of *Chlamydia trachomatis* Endocervicitis in Adolescent Women

Looking for the Right Combination

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• Chlamydial disease in adolescent women is a serious public health problem, but secondary preventive efforts through early detection and treatment are encumbered by the cost and complexity of mass screening. This study was undertaken to identify clinical predictors of infection that might narrow the scope of screening adolescent populations. Demographic/clinical data and endocervical smears for the direct-specimen fluorescein-conjugated monoclonal antibody test for *Chlamydia trachomatis* were collected from 244 consecutive women, 21 years of age or less, attending an adolescent health clinic. Positive direct-specimen fluorescein-conjugated monoclonal antibody test for *C trachomatis* results were associated with a past history of chlamydial infection, multiple sexual partners, sexual contact with men with urethritis, nonuse of condoms, metrorrhagia, exocervicitis, mucopurulent endocervical discharge,

abnormal cervical cytologic features, and isolation of *Neisseria gonorrhoeae* from the endocervix. These variables were entered into a discriminant analysis to predict direct-specimen fluorescein-conjugated monoclonal antibody test for *C trachomatis* results. The discriminant function was statistically significant but explained only 17% of between-group variance. Two variables alone, exocervicitis and partners with urethritis, correctly predicted direct-specimen fluorescein-conjugated monoclonal antibody test for *C trachomatis* results in 79% of all cases (negative predictive value 90%; positive predictive value 35%). When routine screening with reliable laboratory tests is not feasible, selective testing or empirical treatment of adolescent women with either risk factor may be cost-effective alternatives.

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Sexually transmitted diseases in adolescent populations are an increasingly urgent public health concern, and illnesses related to *Chlamydia trachomatis* are among the most prevalent, damaging, and costly. Three to four million Americans are infected each year, accounting for annual health expenditures in excess of \$1 billion.¹ As compared with other subpopulations, young women between the ages of 15 to 21 years have the highest prevalence rates² and are especially vulnerable to

the adverse reproductive consequences of infection, including infertility, ectopic pregnancy, and maternal and infant morbidity and mortality.

Two major problems impede an effective public health response through early detection and treatment³: (1) many, if not most, chlamydial endocervical infections escape attention because they are asymptomatic; and (2) mass screening is cumbersome and expensive. In as many as two thirds to three quarters of infected women, objective signs of cervical inflammation are absent.^{4,6} Physical signs, if present, are nonspecific and can be associated with a variety of other sexually transmitted pathogens.⁷ Consequently, the Centers for Disease Control¹ and a National Institute of Allergy and Infectious Diseases fact sheet⁸ have advocated, respectively, selective screening of persons at high risk (en-

compassing a large proportion of sexually active adolescent women) and annual screening of sexually active women under 35 years of age.

There has been considerable discussion regarding the appropriate selection and use of laboratory screening tests. In many laboratories, the "gold standard" tissue culture method is relatively more costly, technically difficult, and slower^{3,9,10} than other diagnostic tests. Yield is influenced by methods of endocervical sampling¹¹ and transport,¹ contamination with viruses or bacteria,¹ the possible presence of endocervical toxins,¹² or other factors. Despite its theoretically absolute sensitivity, actual-use sensitivity in clinics may be as low as 70% to 80%.^{10,13} Antigen detection assays offer relatively speedier, less costly, and less complicated alternatives,¹ but they are generally less accurate than tissue culture methods in research settings. Specificity, sensitivity, and predictive value apparently vary with the risk characteristics of populations, and, in general, they perform best where disease prevalence is high.³

Given the complexities and costs of screening programs, selective testing of women at high risk, based on reliable clinical indicators, has theoretical and practical appeal. A preselection of "at risk" women for specific laboratory diagnosis would improve the predictive value of tests and reduce costs. These considerations are particularly salient to adolescent patients, given their limited financial resources and high risk for disease. Toward this end, investigators have identified a number of potentially useful associations between endocervical *Chlamydia* infection and subjective and objective clinical findings, including clients' ages,^{5,14,15} race,^{5,16,17} socioeco-

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conomic status,⁵ nulliparity,⁵ numbers of sexual partners,^{14,16,18,19} oral contraceptive use,^{5,15} barrier contraception nonuse,^{14,16,20} previous or concurrent history of sexually transmitted diseases,^{2,16,20,21} contact with infected partners,^{2,20} dysuria,^{2,22} vaginal discharge,¹⁸ cervical ectopy,^{19,23} cervical erythema/edema/friability/mucopurulent discharge,^{5,14,15,18,21,24,25} uterine tenderness,^{12,16} and cervical cytologic atypia.^{24,26}

Because these variables are numerous and interrelated, various investigators^{5,14,18,26} have used multivariate statistical techniques to search for a small number of independent, sensitive, specific, and clinically useful predictors of infection. One study¹⁸ used interview data from consecutive clients in a youth clinic, but several others relied on data from a convenience sampling of clinic volunteers²⁶ or from survey completion by clinic attendees,^{5,14} in low prevalence areas (<15%), with combined adult and adolescent populations. So far, results are mixed. This study was intended to advance understanding of clinical indicators of *C trachomatis* endocervical infection in an exclusively adolescent, sexually active population. We hypothesized that demographic data, self-reported sexual behavior, symptoms and signs, and ancillary laboratory studies would be helpful in distinguishing infected from noninfected adolescents.

SUBJECTS

Subjects were 244 consecutive, sexually active women, 21 years of age or less, who required pelvic examination for any reason at a community-based adolescent health facility during a 15-month period in 1986 and 1987. Excluded from the sample were women who were treated for documented or suspected *C trachomatis* infections or who received any antibiotic therapy during the preceding 6 months. Routine screening for chlamydial infection was not available at the site before the study began. Subjects gave written consent to study procedures, in compliance with institutional review board requirements. Only 1 woman refused to participate.

MATERIALS AND METHODS

Clinicians collected and recorded demographic, sexual behavior, and medical data using a semistructured interview format. All variables that were known to be associated^{2,5,14,26} with infection were elicited (see Table 1 for major variables). Clinicians were four physicians and seven nurse practitioners who were skilled in adolescent gynecologic

care. All subjects underwent pelvic examination and had endocervical smears obtained for the direct-specimen fluorescein-conjugated monoclonal antibody test for *C trachomatis* (DFA). Selection of this test was influenced by practical considerations regarding specimen handling and transport at the community clinical site. Other laboratory studies were obtained, as indicated by the reason for the visit or clinicians' judgment.

Clinicians were individually instructed in appropriate data and specimen collection. Endocervical smears for DFA were obtained after sampling for cervical cytologic features and endocervical gonorrhea culture. The exocervix was cleaned with a large cotton swab. A small cotton-tipped swab was inserted into the cervical os and rotated for at least 15 seconds. The swab was rolled onto a glass slide, air dried, fixed with acetone, and transported for processing. Direct immunofluorescent staining with fluorescein-conjugated monoclonal antibody (DSA Laboratory, Panorama City, Calif) was performed according to the manufacturer's instructions. The presence of intact epithelial cells indicated the adequacy of specimen collection. Slides were scored positive if 10 or more distinct, apple-green, fluorescein-stained chlamydial particles were observed. Only one patient required repeated testing because of initially indeterminate results.

To avoid a "training effect" (ie, learning to associate particular clinical findings with infection), clinicians remained blind to the DFA results and were encouraged not to modify their usual approach to examination, diagnosis, and treatment. All subjects with positive DFA results who escaped clinical detection and treatment during their visits received free follow-up care by one of the investigators (S.E.A.). As an added incentive for careful data collection, clinicians were told that their results might be analyzed in relation to other examiners'.

Statistical Methods

Associations between DFA results and demographic/clinical variables were studied by contingency tables, χ^2 , and *t* tests. Normal and ordinal variables were analyzed with the χ^2 test. Interval data were analyzed by *t* tests, after testing the assumption of equal variances. Based on the outcome of univariate analyses, variables were selected for a discriminant analysis to predict DFA results. All tests were performed with SPSS-X software. The designated level of statistical significance was $P < .05$.

RESULTS

Sample Characteristics

Participants were 244 sexually active young women, 13 to 21 years of age

(mean, 17.86 years). Almost all (94%) subjects were white. Eighty-five percent of participants claimed less than \$6000 per year in personal income. Almost all of the others earned less than \$10 000. Reasons for clinic visits were routine annual pelvic examinations (32%), initial family planning examinations (34%), suspected sexually transmitted diseases (19%), or pregnancy (21%). Miscellaneous other problems, primarily menstrual or oral contraceptive complications, accounted for about 10% of visits.

All but two participants had sexual intercourse during the previous year. Almost half of the sample reported only one sexual partner during the year; the remainder were almost equally divided among women with two partners or with three or more partners. Only 2.5% of participants reported having over 10 partners during the year. The most popular forms of birth control were oral contraceptives (used by 41% of the sample) and/or condoms (27%). Thirty percent of participants had never used a reliable contraceptive method.

Laboratory Results

Fifteen percent (36/244) of endocervical smears were positive by DFA. *Neisseria gonorrhoeae* was isolated from 2% (5/228) of endocervical cultures. *Trichomonas vaginalis* was identified in 5% (4/88) of microscopic examinations of vaginal discharge. A preponderance of clue cells (in 17%) and yeast forms (in 27%) were also noted in specimens of vaginal discharge. All syphilis serologic tests were negative. Six percent (13/210) of Papanicolaou smears were abnormal (class IIa or above). Eight percent (19/244) of participants had positive urine or serum pregnancy tests.

Based on clinical findings, examiners correctly predicted 39% (14/36) of positive DFA smears, and all but one of these suspected infections were treated at the initial visit. Of the 208 negative DFA results, 184 (89%) were accurately predicted. The positive and negative predictive value of clinicians' impressions were respectively 37% (14/38) and 89% (184/206).

Univariate Analyses

Comparisons between positive and negative DFA groups are detailed in

Table 1.—Demographic and Clinical Variables in Relation to Direct-Specimen Fluorescein-Conjugated Monoclonal Antibody Test for *Chlamydia trachomatis* (DFA) Results

Variable	Positive DFA Results (n=36), No. (%) of Patients	Negative DFA Results (n=208), No. (%) of Patients	Value*	df	P
Mean age, y	17.46	17.86	0.02†	242	.99
Race					
W	34 (94.4)	196 (94.2)	6.8	4	.14
Other	2 (5.5)	12 (5.7)			
Reason for visit					
Annual examination	15 (41.7)	63 (30.3)	1.8	1	.17
New family planner	9 (25)	73 (35.1)	1.4	1	.24
Suspected sexually transmitted disease	9 (25)	38 (18.3)	0.9	1	.34
Suspected pregnancy	9 (25)	43 (20.7)	0.5	2	.77
Other	5 (13.8)	25 (12)	0.3	1	.58
Month of visit					
Sep-Nov	17 (47.2)	56 (26.9)	9.7	3	.02
Dec-Feb	9 (25)	48 (23.1)			
Mar-May	1 (2.8)	41 (19.7)			
Jun-Aug	9 (25)	63 (30.3)			
Contraceptive use					
Condom (ever use)	8 (22.2)	58 (27.9)	0.5	1	.48
Condom (always use)‡	2 (5.6)	32 (15.4)	2.4	1	.11
Oral contraceptive	18 (50)	81 (38.9)	1.6	1	.21
None	12 (33.3)	60 (28.8)	0.3	1	.58
Mean annual No. of sexual partners	3.7	2.6	0.8†	235	.42
>1 Annual sexual partner‡	22 (62.9)	98 (48.5)	2.5†	1	.11
Previous gonorrhea	0 (0)	6 (2.9)	1.1	1	.30
Previous <i>Chlamydia</i> ‡	4 (11.1)	8 (3.8)	3.5	1	.06
Partner with urethritis‡	4 (11.1)	4 (1.9)	8.2	1	.004
Symptoms					
Vaginal discharge	13 (36.1)	57 (27.4)	1.1	1	.28
Metrorrhagia‡	7 (19.4)	10 (4.8)	10.1	1	.0015
Dyspareunia	3 (8.3)	11 (5.3)	0.5	1	.46
Urinary frequency	4 (11.1)	21 (10.1)	0.03	1	.85
Dysuria	2 (5.6)	6 (2.9)	0.7	1	.41
Abdominal pain	4 (11.1)	37 (17.8)	1.0	1	.32
Signs					
Exocervical erythema, edema, friability‡	15 (41.7)	28 (13.5)	16.8	1	.0001
Mucopurulent cervical discharge‡	6 (16.7)	12 (5.8)	5.3	1	.02
Cervical motion tenderness	2 (5.6)	5 (2.4)	1.1	1	.3
Ectropion	9 (25.0)	44 (21.2)	0.3	1	.6
Abnormal vaginal discharge	11 (30.6)	43 (20.7)	0.2	1	.19
Uterine/adnexal tenderness	3 (8.3)	17 (8.2)	0.001	1	1.0
Abdominal tenderness	3 (8.3)	18 (8.7)	0.004	1	.94
Laboratory					
Wet preparation					
<i>Trichomonas vaginalis</i>	0 (0)	4 (5.6)	1.0	1	.32
Yeast	4 (23.5)	20 (28.2)	0.1	1	.69
>30% clue cells	1 (5.9)	14 (19.7)	1.9	1	.17
Positive culture <i>Neisseria gonorrhoeae</i> ‡	3 (8.8)	2 (1.0)	8.2	1	.004
Abnormal Papanicolaou test‡	3 (10)	10 (5.6)	6.7	2	.03
Positive pregnancy test	4 (44.4)	15 (27.3)	1.3	1	.25

*Values correspond to χ^2 computation, unless specified otherwise.

†Values correspond to *t* test computation.

‡Variable entered into discriminant analysis.

Table 1 and summarized here. Subjects with positive results were more likely than participants with negative results to report multiple sexual partners during the previous years ($P = .11$) and less likely to report consistent use of condoms ($P = .11$), although these findings did not reach the level of statistical significance ($P = .05$). Statistically significant seasonal differences in infection were noted. Positive DFA results were more prevalent in the fall (23%) and winter (16%) than during the spring (2.8%) and summer (12.5%) months. A greater proportion of positive DFA subjects reported previous chlamydial infection ($P = .06$), metrorrhagia (defined as any intermenstrual bleeding [$P = .0015$]), and sexual partners with urethritis (defined as partner's report of chlamydial urethritis or any symptoms of urethritis [$P = .004$]). Positive DFA results were not associated with age, presenting complaint, or oral contraceptive use (vs any nonuse of oral contraceptives). As indicated in Table 1, some genitourinary tract symptoms were more prevalent among infected women but not to the level of statistical significance.

With respect to physical and laboratory findings, subjects with positive DFA results were more likely to have signs of exocervicitis (defined as cervical erythema and/or edema, and/or friability [$P = .0001$]) and mucopurulent discharge from the cervical os (defined as visualization of yellow mucopurulent discharge on a white swab from the endocervix²¹ [$P = .02$]). *Chlamydia* infections also were associated with the isolation of *N gonorrhoeae* ($P = .004$) and the presence of any Papanicolaou test abnormalities ($P = .03$). No participants had fever or adnexal masses on examination. No significant differences between positive and negative DFA groups were noted with respect to pregnancy test results and microscopic examinations of urine and vaginal discharge.

Discriminant Analysis

A discriminant analysis was used to determine whether positive and negative DFA groups could be differentiated by items from the sexual history, symptoms, signs, and laboratory findings. Nine variables that were associated with DFA results at a level of $P \leq .11$

(Table 1) were entered into the analysis. Seven of these were eligible for inclusion, based on $F > 1$ to enter and a tolerance greater than 0.001 (consistent use of condoms and cervical cytologic results were thus excluded). The discriminant function yielded a canonical correlation of .413, $\Lambda = 0.83$, $df = 7$, and $P = .0000$. The proportion of total variance attributable to between-group differences was 17%. Two variables alone, exocervicitis and contact with a partner with urethritis, accounted for approximately 80% of explained variance. Using a scheme that predicted DFA results to be positive if either variable was present, 79% of all cases were correctly classified (sensitivity, 47% [17/36]; specificity, 85% [176/208]; positive predictive value, 35% [17/49]; and negative predictive value, 90% [176/195]).

COMMENT

This study supports previously described associations between chlamydial endocervicitis and clinical findings in sexually active adolescents, including sexual contact with infected or symptomatic male partners, multiple sexual partners, nonuse of condoms, exocervicitis, abnormal cervical cytologic results, mucopurulent cervical discharge, and endocervical gonorrhea. To our knowledge, the associations of chlamydial disease with metrorrhagia or previous infection have not been described, although they are plausible. Metrorrhagia may herald ascending reproductive tract disease or may be related to friability of the cervix. Adolescents with a history of chlamydial infections may not have received adequate treatment (for various reasons), may have been reinfected by untreated partners, or may have acquired new infections from subsequent partners. In any case, it is disconcerting that 4 of the 12 previously infected young women have ongoing evidence of disease. Although the observation is based on small numbers, it merits further study because of the individual and public health implications of repeated or persistent infection.

Clinical data were better than chance alone in predicting DFA results, but they accounted for only 17% of the total variance between positive and negative DFA groups. Predictive variables were more specific than they were sensitive.

A classification scheme based on exocervicitis and sexual contact with a symptomatic partner better indicated the absence of disease than it did its presence. It is possible that errors in data collection or recording influenced results, though no specific problem areas were noted. False-positive or negative DFA test results might have introduced error into the classification of comparison groups, but the effect was likely to be minor. Stamm³ recently reviewed studies comparing DFA with the enzyme-linked immunosorbent assay tests and tissue culture methods. In populations where disease prevalence exceeded 15%, the median sensitivity and specificity were 90% and 95% for the DFA test, and 89% and 95% for the enzyme-linked immunosorbent assay. As compared with the enzyme-linked immunosorbent assay or tissue culture methods, the DFA test permits assessment of specimen quality.¹ Use of tissue culture for diagnosis might have improved the observed correct classification rate of the predictive model, but it also would have introduced uncertainty regarding adequacy of specimen collection and variability in transport time. Finally, the possibility that some other important predictive variables were missed cannot be excluded. For example, additional information regarding duration of oral contraceptive use, partners' sexual histories, or cumulative years of sexual intercourse may have been helpful.

The performance of the discriminant function was less than ideal but was comparable with results from other populations (Table 2). Among the various studies, gonorrhea, cervicitis, and sexual contact with an infected partner have consistently emerged as independently predictive of chlamydial infection. However, individual clinical findings (ie, cervical erythema, vaginal symptoms, or discharge) accounted for only 3.2% to 9.1% of variance between infected and noninfected adolescent women studied by Fisher et al.¹⁸ Schachter and colleagues⁵ found that the presence of one of several risk factors (gonorrhea, endocervicitis, and sterile urinary tract infection) identified only 30 chlamydial infections in their sample, with an overall positive predictive value of 36%. Harrison et al²⁶ re-

ported that two variables, cervicitis and nonuse of barrier contraceptive methods, had 28% positive and 98.4% negative values in predicting tissue culture results. They recommended selective laboratory testing or treatment for women with either finding.

Using a somewhat different approach, Handsfield and colleagues¹⁴ discovered five factors (including age <25 years and nonuse of condoms) that were predictive of infection. Any combination of two resulted in a greater than 4.7% risk of infection, and they recommended selective testing of women with more than one risk factor. This method maximizes the sensitivity (90%) of clinical prediction at the expense of specificity (63%). Accordingly, a projected 65% of their own sample would have been tested, and 90% of infections would have been detected. The advice of Harrison et al²⁰ and Handsfield et al for selective screening might be limited in an adolescent population, such as our own, where less than 14% of clients used condoms consistently, and nearly all would meet criteria for testing.

Had our model been used to pre-screen clients for laboratory studies or empirical treatment, 20% (49/244) of the sample would have been identified as at risk for disease. Overall, 79% of all participants would have been correctly classified by the two variables, but over half of the infections (19/36) would have been unsuspected. However, if the model were applied to a lower prevalence population such as that of Harrison et al²⁰ (8%), its negative predictive value would rise sharply to 95%, and fewer infections would be missed.

CONCLUSION

Responding to the problem of asymptomatic infection, authorities have advised routine screening. However, young patients often are unable to assume the costs, and the need for confidentiality limits billing of parents or third-party payers. Faced with a financial predicament, clinics and practitioners may select the least expensive screening tests, test only "high risk" clients, or simply treat suspected infections (with or without treatment of contacts). Clinicians should be advised of the limitations of these practices.

Without the benefit of specific labora-

Variable	Source, y			
	Schachter et al, ⁹ 1983	Handsfield et al, ¹⁴ 1986	Harrison et al, ²⁰ 1985	Fisher et al, ¹⁸ 1987
No. of subjects	1230	904	162	200
Age range, y	15-44	23.9 ± 5.5	17-45	14-21
Chlamydia prevalence, %	10.7	9.3	8	14
Predictor variables	Gonorrhea Endocervicitis	Age <25 y New sexual partner	Cervicitis No barrier contraceptive	Cervical erythema >3 Sexual partners
	Sterile urinary tract infection	Mucopurulent cervical exudate Endocervical bleeding No barrier contraceptive		Vaginal symptoms Vaginal discharge: color, amount, consistency
Sensitivity, %	30	90	84	...
Specificity, %	94*	63*	81	...
Positive predictive value, %	36	12*	28*	...
Negative predictive value, %	92	97*	98*	...

*Data are calculated from raw data in authors' article.

tory diagnosis, clinicians who participated in this investigation correctly classified 81% of the sample and detected 39% (14/36) of infections. Nine percent (18/208) of subjects with negative DFA results and their partners were suspected to have infection and were treated. By comparison, selective laboratory testing of patients with cervicitis or with presumptively infected male partners would have improved case detection and possibly reduced overtreatment. This approach might be cost-effective in low-prevalence populations. Schachter¹⁰ estimated that 1 in 10 infected women develops salpingitis, at a cost of \$2000 in direct medical expenses. Thus, in a population of 1000 adolescent women where disease prevalence is 8%, the cost of selective screening by our method would equal the price of 176 tests and four cases of salpingitis. According to this simple analysis, less than \$9.71 per person should be spent for cost-effective screening. By the same reasoning, routine testing becomes even more valuable as disease prevalence increases. For example, when 15% of women are infected, the cost of salpingitis would merit per capita expenditures up to \$19.95. Ultimately,

other costs such as the price of infertility or neonatal infection must be factored into the equation.

An alternative cost-saving approach is to treat empirically persons with suspected infections and to test all others. In the study population, this would amount to a 20% reduction in laboratory expenses for screening, and, theoretically, no infections would be missed. However, 15% (32/208) of women with negative DFA results and their partners would have received treatment. Beyond the possible problems associated with medication side effects and misdiagnosis, absence of laboratory confirmation of disease may adversely affect patient compliance with treatment and contact notification.

In conclusion, a number of clinical findings are associated with DFA results in a population of sexually active adolescent women. These findings can be used to discriminate positive and negative DFA groups but explain only 17% of the variance. The specificity of the proposed predictive model exceeds its sensitivity. In adolescent populations where routine screening for *C trachomatis* is not feasible, judicious use of selective testing or treatment of women

with exocervicitis or presumptively infected partners may be cost-effective alternatives.

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High Prevalence Rate of Human Papillomavirus Infection and Association With Abnormal Papanicolaou Smears in Sexually Active Adolescents

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• Human papillomaviruses (HPVs) are associated with neoplastic and malignant lesions of the uterine cervix. Cervical neoplasia is associated with onset of sexual activity at an early age. Therefore, this study sought to define the prevalence rates of HPV infection and cytologic abnormalities in adolescents. Sexually active females 13 to 21 years of age undergoing routine cervical cytologic screening were evaluated in the adolescent clinic of an urban hospital. Cells collected by cervicovaginal lavage from 249 subjects were analyzed for HPV DNA by Southern blot hybridization with probes for HPV types 6/11, 16, and 18. The HPV DNA was detected in 95 (38.2%) of 249 patients. Teenagers between the ages of 13 and 18 years with multiple lifetime sexual partners were at higher risk for HPV infection (38/71 [54%]) compared with patients of the same age who had only a single partner (25/74 or [34%]). Twenty (8.3%) of 241 patients had abnormal Papanicolaou smears with atypia, koilocytosis, or low-grade cervical intraepithelial neoplasia. Cytologic abnormalities were detected in 16 (17%) of 94 adolescents with HPV present, but in only 4 (2.7%) of 147 of the uninfected patients. Thus, HPV emerged as a common pathogen in female adolescents, and infected patients are at increased risk for cervical epithelial abnormalities.

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Human papillomaviruses (HPVs) have been implicated by molecular hybridization studies in the pathogenesis of cervical intraepithelial neoplasia¹⁻⁶ and invasive cancer of the uterine cervix.⁶⁻⁸ Most research in this area has focused on adult women, since invasive cervical cancer rarely occurs before 30 years of age. However, coitus^{9,10} and pregnancy at a young age¹¹ are risk factors for cervical cancer that relate primarily to adolescents.

While many studies have attempted to explore the importance of HPV infection in adult women, including those without cervical lesions,¹² little information has specifically concerned adolescents with limited years of sexual exposure.¹³ The present study was designed to determine the prevalence rate of and potential risk factors for cervical and vaginal HPV infection in sexually active female adolescents. Papanicolaou (Pap) smears were obtained to determine the relationship between HPV infection and cervical abnormalities. Demographic and behavioral information was used to compare the descriptive epidemiologic characteristics of HPV-positive and HPV-negative individuals.

PATIENTS AND METHODS

Patient Selection

Sexually active female adolescents who were due to have a routine annual Pap smear or in whom cervical cytologic screening was otherwise clinically indicated (eg, history of abnormal vaginal bleeding or possible cervicitis) were eligible for inclusion in the study. The patients, 13 to 21 years of age, were seeking gynecologic care at the Adolescent Ambulatory Service of the Montefiore Medical Center, Bronx, NY, from February 1986 through April 1988. The protocol was ap-

proved by the Institutional Review Board and Research Committee of the medical center.

Written informed consent was obtained from 264 of 273 eligible patients. In 4 patients, specimens were inadequate for HPV determination, and 11 others did not have cervicovaginal lavage on the day of their visit. Thus, the study group consisted of a total of 249 patients who had HPV assessment. Eight patients without Pap smears were excluded from the analyses concerned with cytologic findings. Characteristics of the study subjects are shown in Table 1. The sample subjects were 42% (105) black, 42% (104) Hispanic, 14% (34) white, and 2% (4) from other ethnic backgrounds.

The patients enrolled in the study were seeking gynecologic care on the day of the visit for a variety of reasons that included contraception (45%); problems likely to be related to a sexually transmitted disease (STD) or urinary tract infection, such as genital lesion (excluding warts), dysuria, vaginal discharge (31%); menstrual disorders or abdominal pain (18%); diagnosis of pregnancy or follow-up care after an abortion (9%); and genital warts (2%). One patient had been referred for an abnormal Pap smear.

Clinical Examination, Specimen Collection, and Cytologic Evaluation

Clinical and sociodemographic information was collected through patient interviews and a review of the medical records. Assessment of current or past pregnancy was made by clinical interview and chart review. A serum β -subunit of human chorionic gonadotropin assay was used to confirm pregnancy when either the physical examination or histology suggested pregnancy.

The Pap smears were obtained with a cotton swab from the endocervical canal and by rotating a plastic spatula 360° over the exocervical surface. Smears were evaluated by the cytopathologists at the Montefiore Medical Center who were unaware of patient HPV status. A Pap smear was considered

Table 1.—Characteristics of Study Participants

Characteristic	All Subjects				HPV*-Positive Subjects				HPV-Negative Subjects			
	Mean	SD	Range	N	Mean	SD	Range	N	Mean	SD	Range	N
Chronological age, y	17.9	1.6	13-21	249	17.7	1.5	14-21	95	18.0	1.7	13-21	154
Gynecologic age,† y	5.7	2.1	0-11	247	5.6	2.1	0-11	95	5.8	2.1	1-10	152
Duration of sexual activity, y	2.5	1.9	0-10	244	2.7	2.0	0-10	93	2.3	1.9	0-10	151
Age of Menarche, y	12.2	1.6	8-16	247	12.1	1.7	8-16	95	12.2	1.6	9-16	152
Age of first intercourse, y	15.4	1.9	6-20‡	244	15.0	2.0	6-19	93	15.7	1.8	8-20	151

*HPV represents human papillomavirus. No significant differences occurred between infected and uninfected subjects.

†Gynecologic age was chronological age minus age at menarche.

‡Three patients reported first coitus during sexual abuse before the age of 12 years.

be abnormal when atypia, koilocytosis, or epithelial cells suspicious for cervical intra-epithelial neoplasia were present.

Cultures for *Neisseria gonorrhoeae* were obtained in 225 (90.4%) of 249 patients, using modified Thayer-Martin medium, excluding those with a recent negative culture. Testing for *Chlamydia trachomatis* was performed on 138 (55.4%) of 249 patients with either the direct fluorescent monoclonal antibody test or a McCoy cell culture using confluent monolayers on a coverslip.¹⁴ During the first 16 months of the study, tests for *C trachomatis* were performed on 96 patients with identifiable risk factors for this infection, whereas during the latter part of the study, an evaluation for chlamydial infection became a part of the routine clinical assessment.

Cervicovaginal lavage was used to obtain exfoliated cervical cells for molecular detection of HPV DNA.¹⁵ The cervix was lavaged with 10 mL of 0.9% saline solution using a syringe fitted with a 14-gauge Teflon catheter. The fluid in the posterior fornix was aspirated and transferred to a centrifugation tube containing 1 mL of 0.5 mol/L edetic acid and stored at 4°C.

Detection of HPV DNA by Southern Blot Analysis

The methods used in this study were previously described.¹⁵ Briefly, DNA was extracted from the cervicovaginal cell pellet and purified by phenol chloroform extraction. Five to ten micrograms of DNA was digested with *Pst* I. Southern blot was performed using gel-isolated HPV DNA probes labeled with phosphorus 32 from HPV types 6/11, 16, and 18. The HPV DNA type was determined by a combination of the *Pst* I restriction pattern and the hybridization specificity with different HPV DNA-type probes. The DNA hybridization results were determined without the knowledge of other study results or individual patient information.

Data Analysis

Epidemiologic, clinical, and laboratory data were coded and analyzed with commer-

cial software statistics packages. Frequency distributions, cross tabulations, and descriptive summary statistics were calculated. The χ^2 test (with the Yates' continuity correction for 2×2 tables), comparisons of two means, comparisons of two proportions, and Fisher's Exact Test were used for comparing characteristics of HPV-positive and HPV-negative subjects.¹⁶ Mantel-Haenszel summary odds ratios (OR_{MH}) were calculated for the relationship between HPV infection and patient age to control for the number of sexual partners.¹⁷

RESULTS

The prevalence rate of HPV infection in the 249 patients was 38.2%. An example of HPV DNA detection and typing by restriction analysis and molecular hybridization is shown in Fig 1. Samples 2, 4, 5, 7, 9, 11, 13, 15, 16, and 18 contain HIV DNAs and demonstrate the marked heterogeneity of types detected. In the 95 subjects with infection, HPV 6 or HPV 11 was found in 6 patients (6%), HPV 16 was found in 15 patients (16%), HPV 18 in 14 individuals (15%), and HPV DNA that was partially homologous with HPV 16 was observed in 7 patients (7%). Sixty-four (67%) of the 95 infected subjects had an HPV uncharacteristic for the above types, termed a "related" HPV. Eleven (12%) of the patients had two different HPV types present.

Of the various reasons that patients sought care on the day of their visit, only the presence of condylomata acuminata was more likely to be associated with the presence of HPV ($\chi^2=6.26$, $P=.018$, excluding patients with condylomata acuminata). The percentages of HPV-positive patients within each of the presenting complaint groupings are shown in Fig 2.

Unexpectedly, for the group the

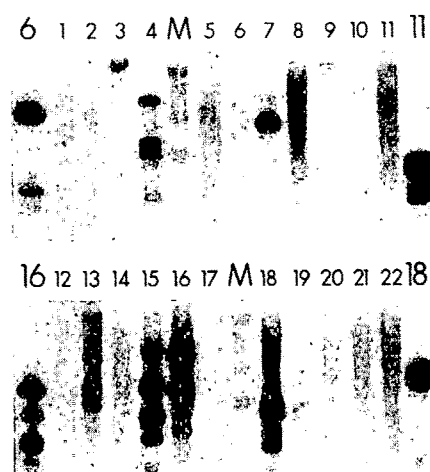


Fig 1.—Detection of human papillomavirus (HPV) DNA by *Pst* I restriction and Southern blot analysis using a mixed probe of HPV types 11, 16, and 18. Sample DNAs are indicated by small numbers 1 through 22. The HPV DNA types 6, 11, 16, and 18 (20 ng) were digested with *Pst* I and served as the positive controls as indicated in the first and last lanes of each panel. Lanes designated M (size marker) contain phosphorous 32-end-labeled lambda-DNA-*Hind*III fragments.

number of lifetime sexual partners did not reach a statistically significant association with HPV infection: 61 (66%) of 92 of the HPV-positive patients had had more than one lifetime partner, while 81 (54%) of the 151 uninfected patients had more than one partner ($P=.07$). However, the younger patients, 13 to 18 years of age, were nearly twice as likely to be infected with HPV than those 19 to 21 years old, a finding that was mainly attributable to patients with more than one lifetime sexual partner (Table 2)

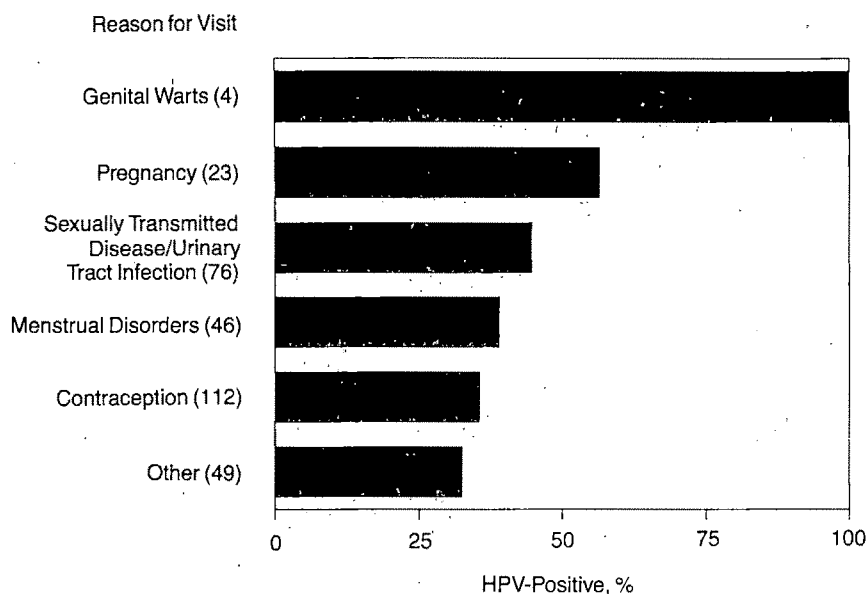


Fig 2.—Percentages of patients positive for human papillomavirus (HPV) among the total number of patients within each chief complaint grouping. The number of patients within each group is shown in parentheses. The sexually transmitted disease group does not include patients with genital warts.

Table 2.—Proportion of Patients Infected With Human Papillomavirus (HPV) According to Number of Sexual Partners by Chronological Age*

Chronological Age, y	HPV-Positive Patients, No. (%)		Total
	Single Partner	Multiple Partners	
13-15	5/15 (33)	4/6 (67)	9/21 (43)
16-18	20/59 (34)	34/65 (52)	54/124 (44)
19-21	9/33 (27)	23/71 (32)	32/104 (31)

*Mantel-Haenszel summary odds ratio = 1.9; 95% confidence interval = 1.1 to 3.4.

(OR_{MH} = 1.9; 95% confidence interval [CI] = 1.1 to 3.4).

Chlamydia trachomatis was found in 24 (17%) of 138 persons screened. *Neisseria gonorrhoeae* was found in 5 (2%) of 225 individuals tested. *Chlamydia trachomatis* was found in 18 (18.8%) of 96 patients in the selective first part of the study compared with 6 (14.3%) of 42 patients seen in the latter part of the study when testing was used more routinely (this finding was not statistically significant). Among persons with either gonococcal or chlamydial infection, 8 (30%) of 27 were also infected with HPV, while among persons without *N. gonorrhoeae* or *C. trachomatis*, 46 (41%) of 111 were infected with HPV ($P = .4$).

Twenty (8.3%) of 241 patients had abnormal Pap smears. Six patients dem-

onstrated cytologic changes that were suspicious for low-grade cervical intraepithelial neoplasia, 2 had koilocytosis or other findings suggestive of condyloma, and 6 had smears in which low-grade cervical intraepithelial neoplasia could not be distinguished from koilocytosis. The remaining 6 patients had cellular atypia that was not specific. Cervical cytologic abnormalities were detected in 16 (17%) of 94 adolescents with HPV present, but in only 4 (2.7%) of 147 of the uninfected patients (OR = 7.3; 95% CI = 2.4 to 22.7). When the patients with atypia that was not specific were excluded from the analysis, the strongly positive relationship between HPV infection and abnormal Pap smears remained (OR = 11.0; 95% CI = 2.4 to 50.4). No relationship was

found between the patient's age or number of sexual partners and the likelihood of having an abnormal Pap smear.

Abnormal Pap smears were found in 2 (40%) of 5 patients with HPV type 6/11 present, in 3 (20%) of 15 with type 16, in 2 (14%) of 14 with type 18, in 1 (14%) of 7 with a 16-related type, and in 11 of 64 (17%) with other related HPV types (Fig 3). The HPV type 6/11 was more common among patients with condyloma acuminatum (3 [30%] of 10) than in patients without warts present (3 [3%] of 96, $P = .01$). Eight patients had condylomata acuminata of the vulva or vagina on physical examination, all of whom had a positive result for HPV on their cervicovaginal lavage specimen. Three (37.5%) of these 8 subjects had an abnormal Pap smear, while 17 (7.4%) of 231 of those without condylomata present had an abnormal Pap smear ($P < .05$).

Patients infected with HPV were more likely to have a history of pregnancy, although this association did not reach statistical significance. Forty-two (44.7%) of 94 adolescents who had been pregnant at least once had HPV infection, whereas only 50 (33.6%) of 149 of the nulligravida patients had HPV DNA detected ($P = .1$).

COMMENT

Urban female adolescents in the United States have a mean age of first coitus of 16 years,¹⁸ and as many as 4% of sexually active teenagers and young adults have cervical intraepithelial neoplastic lesions.^{19,20} In addition, more than 1 million pregnancies occur annually among teenagers in the United States.²¹ Additional risk factors for cervical cancer common among some young people include having multiple sexual partners, having a high-risk partner, and cigarette smoking.^{11,22}

Furthermore, sexually active adolescents are at high risk for STDs. *Neisseria gonorrhoeae* has been found in 1% to 18%²³⁻²⁵ and *C. trachomatis* in 14% to 26%²⁶⁻²⁹ of adolescents. A trend over the past 20 years toward an increased frequency of condyloma acuminatum has been reported in all age groups, including some of the highest rates among adolescents.³⁰

The strikingly high prevalence rate of 38% indicates that HPV may be the

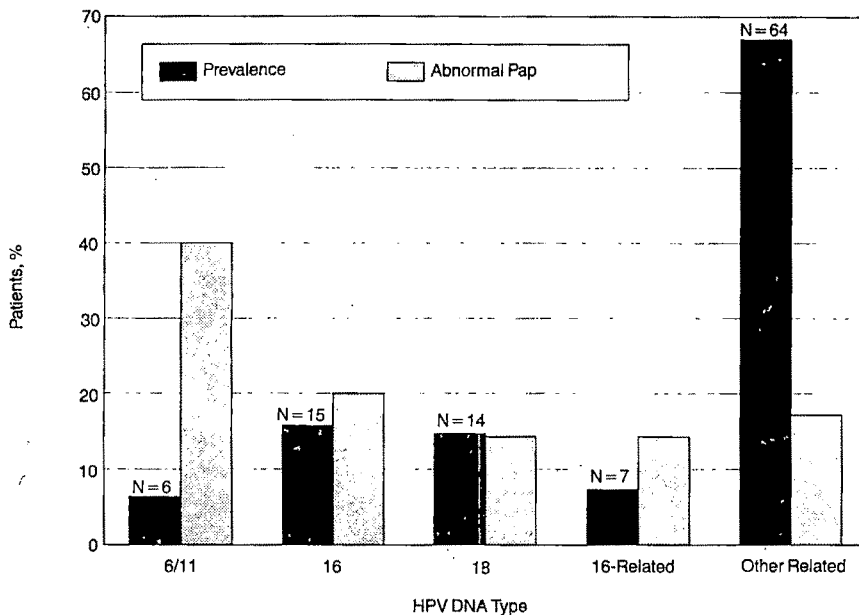


Fig 3. — Percentage of each human papillomavirus (HPV) DNA type among the 95 patients with HPV infection (11 patients had two HPV DNA types); for each HPV DNA type, the percentage of patients with an abnormal Papanicolaou (Pap) smear is listed. N indicates the number of patients with each HPV DNA type.

most common STD among female adolescents seeking care within an urban teaching hospital clinic. The investigation of other populations of adolescents will be required to determine whether this virus is as common among diverse groups of sexually active adolescents. The methods used here, including the cervicovaginal lavage for cell harvesting³¹ and Southern blot molecular hybridization for viral DNA detection, probably account for the higher HPV prevalence rate than has been reported by other investigators.¹⁸ (Only 1.6% of the lavage specimens provided insufficient cell quantity for Southern blot experiments in our study.)

Some of the sociodemographic and behavioral characteristics of our patients differ from other groups of young people. Yet, the adolescents in the present study were seeking care for the full range of gynecologic and family-planning issues. Less than one third of the patients had a chief complaint directly related to an STD. Moreover, those patients whose visit was prompted by a symptom possibly related to an STD were not more likely to be HPV-positive. The rates we observed for gonorrhea and *Chlamydia* are consistent with published studies in comparable

populations of young people.^{23,26,28} Furthermore, the mean age of menarche and frequency of previous pregnancy among our patients were similar to reports of other populations, suggesting that our results indeed may be applicable to other urban youth.^{18,32}

The high-risk status for STDs associated with adolescence is likely to be related to a combination of behavioral, psychosocial, and biological factors that also have a bearing on infection with HPV and the development of cervical neoplasia. Sexual experimentation, poor use of barrier methods of contraception, and inadequate use of health care services because of fears regarding confidentiality are common in adolescence.³³ The transformation zone of the cervix, the area where the columnar cells undergo metaplastic transformation, is larger during adolescence than later in life. This zone is not only more susceptible to infection with sexually transmitted pathogens but is also known to be the area from which most cervical cancers originate.³⁴ The strong association observed in our patients between HPV infection and cytologic abnormalities is consistent with findings from multiple studies of adult women.

It is not surprising that the older pa-

tients in the study (those at least 19 years of age) had been sexually active for more years and reported having more lifetime sexual partners. However, of interest is the finding that young age was associated with HPV infection in patients who had more than one lifetime sexual partner. One implication from this observation is that young female adolescents (but not necessarily older adolescents) who have had multiple sexual partners should be considered at higher risk for STDs.

The age-dependent association of number of sexual partners with HPV was not found for chlamydial infection or gonorrhea. While *C trachomatis* and *N gonorrhoeae* are certainly also transmitted through sexual contact, they are more likely than HPV to produce symptoms that prompt a medical visit and effective treatment. An HPV infection is typically asymptomatic (only 8% of the HPV-positive patients had condyloma acuminatum) and, in some patients, may persist over time.³⁵ Even when infection with HPV is recognized, treatment modalities are often unsuccessful. Our patients' knowledge regarding a history of STDs was not found to be reliable (data not shown). Perhaps if such data were available, similar associations might be found between ever having had *C trachomatis* or *N gonorrhoeae* and the presence of HPV, as well as with their number of lifetime sexual partners.

A number of considerations may have contributed to the fact that we did not detect a statistically significant association between HPV infection and previously reported risk factors for cervical cancer in the population as a whole. It may be assumed that both HPV-infected and uninfected young women share certain features of adolescence within an urban environment. Therefore, differences in the behavioral characteristics between the infected and uninfected groups may be too small to reach statistical significance with the present sample size. Another possibility is that many of the male partners of our patients may have had numerous sexual contacts. In that case, the young women who reported having had only a single lifetime partner, but whose partner had had numerous sexual contacts, might nonetheless have had the same degree

of exposure to sexually transmitted pathogens as the patients who reported having had many partners.

The presence of HPV may serve both as a sensitive indicator of sexual exposure and of risk for cervical abnormalities. Also, since concurrent infection with multiple STDs is common, the discovery of one STD in a patient may serve as a warning to the likely presence of others. This is of particular concern, given current apprehension regarding the risk for acquired immunodeficiency syndrome in the adolescent population.³⁶

The high prevalence rate of HPV observed in our study is distressing. Since

HPV infection is usually asymptomatic, identification and treatment of contacts are more difficult. Such HPV-infected adolescents are at far higher risk of cervical cytologic abnormalities than those without this virus present. It remains uncertain whether these HPV-infected persons are at substantially higher risk for development of cervical dysplasia and invasive cancer later in life. Cofactors such as cigarette smoking, other STDs, and lack of access to health care may be important. Prospective follow-up of both infected and uninfected adolescents, both with and without cytologic abnormalities, should contribute to our understanding of the natural his-

tory of HPV infection in young people.

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Study of Virus Isolation From Pharyngeal Swabs in Children With Varicella

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• We performed virus isolations from the pharyngeal swabs in 117 children with varicella who were aged from 22 days to 15 years and 70 healthy children who were aged from 3 months to 15 years, by using human embryonic lung cell cultures. Viral isolates were confirmed by an indirect immunofluorescence method or by neutralization with well-characterized antibodies. Five varicella-zoster virus isolates (4.3%), 23 cytomegalovirus isolates (19.7%), five herpes simplex virus isolates (4.3%), and one respiratory syncytial virus isolate (0.9%) were found in the patients with varicella. Ten cytomegalovirus isolates (14.3%), two herpes simplex virus isolates (2.9%), one respiratory syncytial virus isolate (1.4%), and one poliovirus isolate (1.4%) were found in the swabs of the healthy control children. The varicella-zoster virus isolation rate from the pharyngeal swabs in children with varicella was low as compared with the rate from those pharyngeal swabs in the children with cytomegalovirus and herpes simplex virus. No varicella-zoster virus isolates could be found in the swabbed materials after filtration (0.45 μ m). On the other hand, cytomegalovirus and herpes simplex virus could be isolated from the filtrated swabs, as well as from the unfiltered swabs. The method of testing by filtration could have affected the results. (AJDC. 1989;143:1448-1450)

Varicella, caused by primary infection with varicella-zoster virus (VZV), is a common and highly contagious disease of childhood. Varicella-zoster virus is assumed to spread by

droplet nuclei or air droplets, because airborne transmission of varicella in hospitals has been demonstrated.^{1,2} We report the results of our attempts to isolate VZV from the pharynx of patients with varicella; the pharynx is considered to be the main source of infection by the end of the incubation period and during the first days of the exanthem.

SUBJECTS AND METHODS

This study was conducted at the pediatric outpatient clinic of Showa Hospital, Kohnan, Japan. Children in this study comprised patients with varicella and healthy children as controls. One hundred seventeen children with varicella, who had no known underlying diseases and were not receiving immunosuppressive therapy, were aged from 22 days to 15 years (mean age \pm SD, 3.62 ± 2.90 years). Five of these children had varicella during the incubation period. The second group included 70 healthy children who were aged 3 months to 15 years (mean age \pm SD, 4.66 ± 4.48 years). After the project was explained, consent was obtained from the parents.

Pharyngeal swabs were taken from 187 children in both groups in a single instance. The collecting medium was Eagle's minimal essential medium with 10% fetal calf serum that contained some antibiotics (streptomycin, 100 mg/L; penicillin G, 100 000 U/L; ampicillin, 250 mg/L; and amphotericin B, 12.5 mg/L).

The scheme of virus isolation is shown in Fig 1. Human embryonic lung cells between 7 and 20 passage levels were used for the virus isolation study. All swabbed materials, after 4 hours of incubation, at the most, in the collecting medium at 4°C, were directly inoculated onto cell cultures (method A). At the same time, one-half volume of 67 swabbed materials obtained from the patients with varicella and of 37 swabbed materials obtained from the healthy children were inoculated after filtration with a 0.45- μ m filter unit (Millipore, Swinnox-HA, Bedford, Mass) (method B). The cultures were observed daily, and even if no cytopathic effect was observed, the cells were treated with

trypsin and suspended in a maintenance medium. The cell suspension was then mixed with a newly prepared human embryonic lung cell suspension in a growth medium. Observation was continued for a further period of about 3 weeks. When no cytopathic effect was detected at the end of the observation period, the virus isolation was considered to be negative.

Viral isolates were primarily identified by a characteristic cytopathic effect. An indirect immunofluorescence assay was then used for the identification of VZV, cytomegalovirus (CMV), and herpes simplex virus (HSV). The monoclonal antibody, highly specific for VZV, and the polyclonal antibody to HSV were made in the laboratory of one of us (M.T.). The procedures for the preparation of the monoclonal antibody to VZV have been described previously in detail.³ The monoclonal antibodies, commercially available to CMV (Dakopatts, Glostrup, Denmark) and to HSV type 1 or HSV type 2 (Syva, Palo Alto, Calif), also were used. A neutralization test was done for the identification of respiratory syncytial virus and poliovirus with standard, commercially available antisera (Seiken, Tokyo, Japan). In addition, a T-marker test was done against an isolate of poliovirus.

To control the quality of our isolation techniques, the isolation attempts were performed from the vesicular fluid during the first 3 days of varicella. The positive rate of VZV isolation was more than 90% by method A (data not shown).

The frequency data of virus isolation in the two groups were compared by the χ^2 test.

RESULTS

Figure 2 shows that 5 VZV isolates (4.3%), 23 CMV isolates (19.7%), 5 HSV isolates (4.3%), and 1 respiratory syncytial virus isolate (0.9%) were found in the pharyngeal swabs obtained from 117 children with varicella. The cytopathic effect appeared within 7 days in all 5 HSV isolates, but in 2 of the 5 VZV isolates and in 9 of the 23 the CMV isolates, we needed the second subculture for the cytopathic effect appearance. No virus could be isolated from

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Table 1 demonstrates a comparative study of the incidence of the virus isolation from the pharyngeal swabs between patients with varicella and healthy control children. Ten CMV isolates (14.3%), 2 HSV isolates (2.9%), 1 respiratory syncytial virus isolate (1.4%), and 1 poliovirus isolate (1.4%) were obtained from the group of healthy children. With regard to the virus isolation frequency, there was no significant difference between the two groups, except for VZV. The CMV and HSV infections were inapparent in all the CMV- and HSV-positive children in both groups, and the clinical features of varicella did not seem to be explicitly influenced by CMV and HSV. The 7 HSV isolates were all confirmed to be type 1 by the test of neutralization. A child who had been inoculated with a live oral poliovirus vaccine 8 days previously yielded a polio vaccine virus type 2 in the pharynx.

One hundred four swabs in both groups were inoculated onto the cell cultures by two methods at the same time, directly (method A) and after filtration (method B). This comparative study of virus isolation between the filtrated and unfiltrated swabs is shown in Table 2. No VZV could be isolated from the swabs after filtration. In contrast, CMV (93.8%) and HSV (100%) could be isolated from the filtrated swabs, as well as from the unfiltrated swabs.

COMMENT

Although VZV can be readily isolated from the vesicular fluid obtained within the first 3 days of the rash, it is difficult to isolate VZV from the other portions. Recently, we have demonstrated viremia in children with varicella who had no underlying diseases, by using a sensitive human embryonic lung cell culture

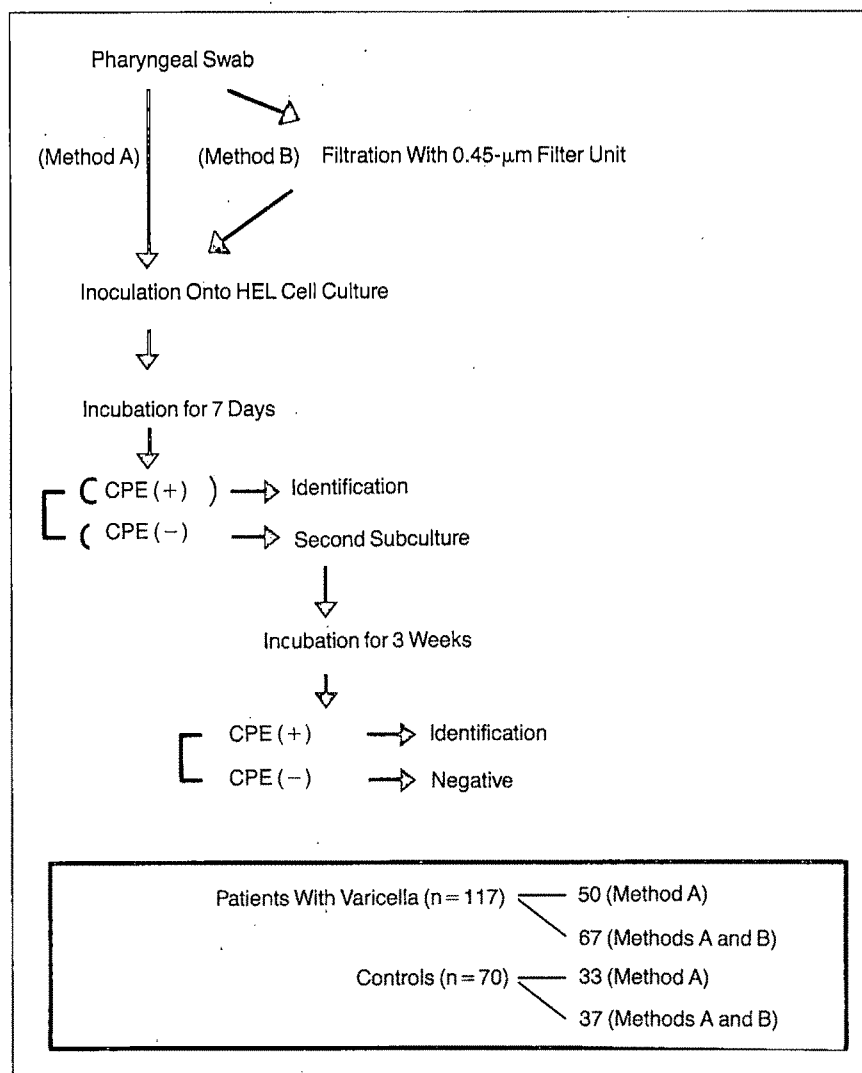


Fig 1. —Scheme of virus isolation. HEL indicates human embryonic lung; CPE, cytopathic effect.

Fig 2.—Virus isolation from patients with varicella. VZV indicates varicella-zoster virus; CMV, cytomegalovirus; HSV, herpes simplex virus; and RSV, respiratory syncytial virus.

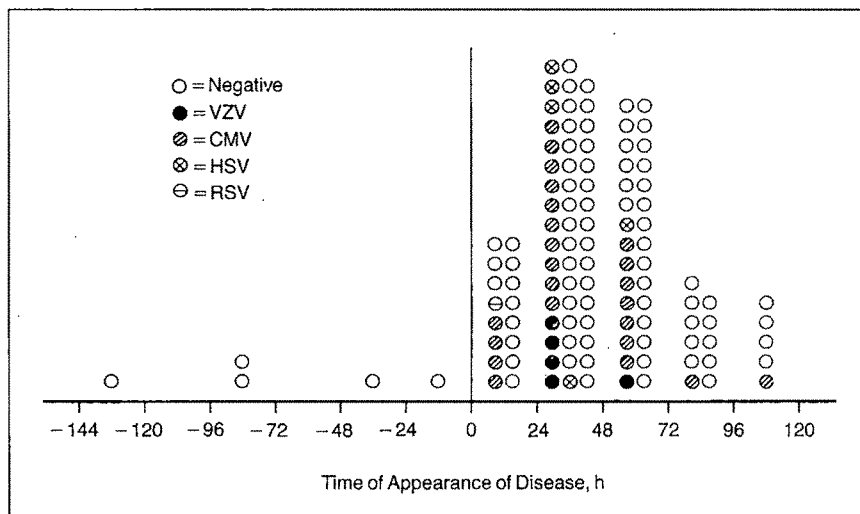


Table 1.—Incidence of Virus Isolation*

	Incidence (%)	
	Patients With Varicella (n = 117)	Controls (n = 70)
VZV	5/117 (4.3)	0/70 (0)
CMV†	23/117 (19.7)	10/70 (14.3)
HSV†	5/117 (4.3)	2/70 (2.9)
RSV†	1/117 (0.9)	1/70 (1.4)
Poliovirus†	0/117 (0)	1/70 (1.4)‡

*VZV indicates varicella-zoster virus; CMV, cytomegalovirus; HSV, herpes simplex virus; and RSV, respiratory syncytial virus.

†Isolation rate was not significantly different by the χ^2 test.

‡The isolated strain was type 2 and the vaccine type.

Table 2.—Comparative Study of Virus Isolation Between Filtrated and Unfiltrated Swabs*

Virus	Filtrated/Unfiltrated Swab Result
VZV (n = 3)	Filtration (+)/filtration (−) = 0/3
CMV (n = 16)	Filtration (+)/filtration (−) = 15/16
HSV (n = 3)	Filtration (+)/filtration (−) = 3/3

*VZV indicates varicella-zoster virus; CMV, cytomegalovirus; HSV, herpes simplex virus.

technique.^{4,6} The viremia has been shown not only during the first few days of varicella but also in the incubation period.⁶

As far as we know, VZV isolation from the pharyngeal area has been reported in a small number of cases. Gold,⁷ Cesario et al,⁸ and Myers⁹ reported one case each. Trlifajova et al¹⁰ reported five VZV strains that were isolated, three from nasal and two from pharyngeal swabs, but their patients with varicella, from whom swabbed materials were taken, had various forms of congenital defects (Down syndrome, alkaptonuria, amaurosis, epilepsy, oligophrenia, hydanoinate syndrome, retinitis pigmentosa, etc), except for two normal individuals. In the present study, we found five VZV isolates on the pharyngeal mucosa at the time of the developing exanthem in normal children with varicella. Nelson and St Geme¹¹ and Trlifajova et al¹⁰ did not isolate VZV from 8 and 57 pharyngeal swabs, respectively, during the preeruption period, and in our study, we also did not isolate VZV similarly from the children during the incubation period.

In our study, 23 CMV isolates (19.7%) were found in the children with varicella, and 10 CMV isolates (14.3%) were found in the healthy control children. Salivary shedding of CMV was observed commonly, as well as urinary shedding. The high incidence of excre-

tion from the pharyngeal swabs in infants diminishes accordingly as the age increases.¹²⁻¹⁵ The positive rates of CMV from the pharyngeal swabs, 14.3% in healthy children and 19.7% in children with varicella, were almost the same as that found in the reports of many researchers.^{10,12-16} As CMV- and HSV-positive isolation rates did not differ significantly between patients with varicella and healthy control children, no evidence was demonstrated that the VZV infection altered the immunologic state of the host and might increase their positive isolation rates.

Epidemiologic data, including an experiment of VZV infection to the common marmoset,¹⁷ suggest that a phase of respiratory tract repose exists. However, the incidence of recovering VZV from the pharynx was low, and the VZV isolates could not be found in the swabs after filtration. The results of our study indicated that a small number of infective VZV particles existed on the pharynx of children with varicella, and that the method of testing by filtration may affect the isolation of VZV. Why the virus is easily isolated from vesicular lesions and elusive in the pharynx poses some interesting questions. It may be possible that the impressive communicability of varicella results simply from the extensive airborne and contact dissemination of the more thermostable virus from the cutaneous vesicles. How-

ever, these reflections are inconsistent with an epidemiologic factor that a patient with varicella may transmit the disease to other susceptible persons from approximately 1 day before the onset of the rash. To confirm those reflections and to resolve this paradox, we will continue with a further isolation study of VZV by using a more sensitive technique, eg, DNA hybridization.

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Transmission of Chickenpox in a School Setting Prior to the Observed Exanthem

Philip A. Brunell, MD

• An epidemic of chickenpox in a class is described. Four children were able to transmit infection prior to the time their rash was observed by their parents. A fifth child was known to have attended school while he had localized varicelliform lesions that were present for 2 days prior to the appearance of the generalized exanthem. It cannot be ascertained whether some of the other children may have had similar lesions that were not observed at the time they attended school. The first classroom case was observed prospectively so that the time of rash was fairly well established. Although he apparently transmitted infection prior to the onset of rash, virus could not be isolated from the respiratory secretion of this child on the day he presumably infected his classmate. Virus was not found in his respiratory secretions or those obtained from his two siblings before or after the onset of rash, although it was recovered from vesicular fluid.

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It is generally assumed that patients with chickenpox are contagious prior to the onset of rash.¹ If these patients are indeed contagious at this time, they must spread varicella-zoster virus from a site other than their skin lesions. It is known that many viral infections are spread via the respiratory tract and that virus can be readily demonstrated in the respiratory secretions of patients with these infections.^{2,3} In spite of the presence of lesions in the mouths of some patients with varicella, isolation of varicella-zoster virus from pharyngeal secretions has been reported only rarely.^{4,5} Systematic attempts by others

either have failed⁶ or met with limited success.^{7,8} We present epidemiological evidence that indicates that patients with chickenpox may be contagious prior to the time their rash is observed. The respiratory tract could not be established as the source of infecting virus as varicella-zoster could not be detected in respiratory secretions of patients with chickenpox.

EPIDEMIOLOGICAL OBSERVATIONS

The index case was a physician who became ill with chickenpox. Onset of the typical varicelliform rash occurred in his three children 13, 14, and 14 days after the lesions were observed on their father's skin. The children were examined thoroughly and specimens of nasal and pharyngeal secretions were obtained daily from the 10th day after exposure to the second day following the rash. The oldest of the three children was first noted to have a varicelliform rash at noon on a school holiday; the rash was not present that morning when he was examined at the time of specimen collection or the previous evening. Consequently, it was assumed that no skin lesions were present the previous day when he last attended school. A postcard inquiry at the time of onset of the first classroom case indicated that (1) none of his classmates had chickenpox previously during the school year, (2) none of his classmates had contact with others with chickenpox in the community, and (3) seven classmates had not had chickenpox.

Chickenpox occurred in five of seven contacts at approximately 2-week intervals; ie, at 17, 28, 43, 57, and 57 days after exposure. In four of the five contact cases, including the physician's child, the rash was discovered while the children were home. In each of these instances, the parents denied that their children had attended school when the rash was present. The mother whose child had the onset of chickenpox at 43 days acknowledged that her son had attended school for 2 days while lesions were present on his neck. Extracurricular exposure was denied in all cases. All five susceptible sibling contacts of

the classroom cases developed chickenpox 2 to 3 weeks after the household exposures.

VIRAL STUDIES

Specimens of vesicular fluid were collected on the second or third day of the rash with capillary pipettes and taken immediately to the laboratory where they were inoculated into cultures of human embryonic lung fibroblasts. Specimens of pharyngeal or nasal secretions were collected with dry cotton swabs. These swabs were placed immediately into screw-capped tubes containing 1 mL of partially frozen (4°C) Eagle's medium. These were taken to the laboratory and the Eagle's medium containing the specimen was transferred to a screw-capped tube containing a cell monolayer from which the tissue culture fluid had been removed. No more than 30 minutes elapsed between the collection of specimens and inoculation of the cultures.

Eagle's minimum essential medium without serum containing 0.15% sodium bicarbonate, 200 U/mL of penicillin, 100 µg/L of streptomycin was used for the collection of specimens and subsequently for maintenance medium. Cultures were observed daily for the presence of cytopathic effect. If the characteristic effect produced by varicella-zoster (V-Z) virus was observed, the specimen was assumed to contain V-Z virus.

The V-Z virus was isolated from vesicular fluid obtained from two of the three physician's children and from 8 of 12 vesicle fluid samples from other patients that were tested in the laboratory during this time. No virus was detected in specimens of pharyngeal or nasal secretions obtained daily from the physician's three children from approximately 4 days before to 2 days after the onset of rash. The isolate from the resident's daughter, Ellen, had been serially passed more than 200 times and was a prototype strain of V-Z virus available from the American-type tissue collection.

COMMENT

The source of the virus that infected the classmate who became ill with chickenpox 17 days following exposure to the

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physician's child could not be ascertained. No skin lesions were known to be present at the time exposure occurred. Although it was assumed that infection was spread from another site or source, a diligent search was made for other contacts and none could be found. Efforts to recover virus from respiratory secretions of the physician's child on the day exposure occurred, moreover, were unsuccessful. It must be assumed that infectious virus was not in the respiratory secretions or that the test system was too insensitive to detect virus that was present. Observations that pharyngeal secretions from children with chickenpox could not be used to transmit infection to other children suggest that infectious V-Z virus might not be present in pharyngeal secretions.⁹

A systematic effort to isolate virus was successful in only 5 of 117⁸ and 2 of 22⁷ throat specimens and 3 of 22 nasal swabs obtained after the onset of rash. No virus was isolated prior to the onset of rash from 56 nasal and 57 pharyngeal specimens.⁷ It was suggested that the isolation only after onset of lesions and its infrequency might indicate that the virus isolated might have been transferred by the fingers of these children.⁷ Alternatively, the tissue culture system used for isolation may not have been sensitive enough to detect small quantities of V-Z virus present in respiratory secretions, although vesicular fluid isolates were obtained readily. In an attempt to increase the chances of isolat-

ing virus in the present study, cultures were inoculated with larger inoculum than is normally used and inoculated 30 minutes after they were collected; nasal as well as throat secretions were also examined for the presence of virus.

Since the classroom cases of chickenpox occurred at intervals of approximately 2 weeks and there were no known extracurricular sources of exposure, these cases were probably serially transmitted. These children spread their infections prior to the time their skin lesions were observed since, except for one child, their parents denied that they had attended school after the onset of rash. One child was known to have attended school while localized lesions were present on his neck. These lesions were present for 2 days prior to the time his generalized eruption was observed. Localized vesicles that had been excoriated were also observed to precede the generalized exanthem in one of the physician's preschool children.

It is possible, therefore, that localized lesions that were not noticed by the parents might have been the source of virus that infected additional children in the classroom. Virus might have been disseminated directly by the fingers of the children at the time the vesicles were broken. Our judgment that chickenpox is contagious prior to the rash is based on reports of similar epidemiological observations. In one of these reports, it was concluded that "infectivity preceding the eruptive stage in this disease

must be of short duration" as removal from a contact case 9 hours prior to onset of chickenpox resulted in diseases, whereas removal 24 hours or more prior to onset did not.¹⁰ Evans¹¹ cited two of his own experiences supporting pre-emptive contagiousness and cited some similar cases.

Although our epidemiological observations do not provide a definitive answer to whether children with chickenpox are contagious prior to the time their rash appears, they certainly indicate that a child might be contagious before the rash is observed. Even when parents made an effort to keep children with rash from school, spread of chickenpox occurred and five of the seven susceptible children in the classroom were eventually infected. Excluding children from school resulted in distributing the cases for a period of several generations. In contrast, all of the susceptible household contacts of the classroom cases developed chickenpox approximately 2 weeks following exposure. In a larger study 383 (87%) of 441 susceptible household contacts developed chickenpox about 2 weeks after the initial household case.¹²

The inevitability of chickenpox in the absence of a vaccine raises questions about the wisdom of keeping children home from school and day care who are otherwise well enough to attend.¹³ The cost of this practice in lost wages of parents who must remain at home with these children approaches \$400 million annually.¹⁴

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Educational Interventions



Hugh D. Allen, MD, Columbus, Ohio
Fredric Burg, MD, Philadelphia, Pa
Harold Levine, MPA, Galveston, Tex
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Purpose.—This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.

Editorial Comment.—*Although national guidelines for the detection of elevated lead levels in children have been developed, how well are they implemented? This study shows how evaluation criteria were developed and then used to judge how well various pediatric teaching programs implemented lead screening practices. See how they apply to your program.*—H.D.A.

Lead Screening at Pediatric Teaching Programs

Karen S. Edwards, MD, Brian W. C. Forsyth, MB, ChB, FRCP

Elevated blood lead levels continue to occur frequently in children, especially among those living in low-income inner-city neighborhoods. As evidence accumulates that the "safe" level of blood lead is lower than previously thought,¹ the ascertainment of all cases of elevated blood lead levels in children becomes even more important.

In 1985, the Centers for Disease Control (CDC), Atlanta, Ga, issued new lead poisoning prevention guidelines that state that ideally *all* children between the ages of 9 months and 6 years should be screened annually for elevated lead levels.² In 1987, the American Academy of Pediatrics (AAP) issued a similar set of guidelines.³ Both sets of guidelines describe the ideal criteria for screening, but then specify a list of priority groupings for screening if the ideal cannot be met. Neither set of guidelines

provides specific recommendations regarding arrangements for the central collection and interpretation of lead screening results or for assuring the proper follow-up of abnormal test results.

The extent to which these recommendations have been incorporated into screening practices at institutions providing health care to urban children is unknown. To our knowledge, there has not been a systematic survey of currently used methods of screening and provision of follow-up for children with elevated blood lead levels. Because the official guidelines provide only priorities for screening (Table 1) rather than a specific definition of groups that must be screened, it was expected that there would be a broad range of application of guidelines.

The purpose of this study was to determine the range of lead screening practices at urban pediatric teaching programs. Teaching programs were studied because their screening practices are likely to be propagated by their graduates and because we assumed that their screening standards would best reflect the latest guidelines. Programs in large cities were chosen to assure that the populations served would include a large proportion of high-risk children (ie, low income, minority, urban).

Programs provided information regarding age at first screening, the frequency of screening, and the extent of centralization of data collection, interpretation, and follow-up. They also provided information about possible impediments to ideal screening practices, such as the use of venipuncture to obtain screening specimens and the lack of institutional guidelines for screening. We requested information regarding the use of the following techniques that

Table 1.—Suggested Priority Groups for Lead Screening²

1. Children aged 12 to 36 months who live in, or are frequent visitors to older, dilapidated housing
2. Children aged 9 months to 6 years who are siblings, housemates, visitors, and playmates of children with known lead toxicity
3. Children aged 9 months to 6 years living in older, dilapidated housing
4. Children aged 9 months to 6 years who live near lead smelters and processing plants or whose parents or other household members participate in a lead-related occupation or hobby
5. Children aged 9 months to 6 years who live near highways with heavy traffic or near hazardous waste sites where lead is a major pollutant
6. All children 12 to 36 months of age
7. All children 9 months to 6 years of age

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sociation; 1986:265-273.

might improve the completeness of screening: on-site free erythrocyte protoporphyrin (FEP) determination, the use of fingerstick capillary specimens, and a review by institutions of their own screening programs.

METHODS

The largest residency training programs (judged by the number of positions available) in northeastern US cities with populations greater than 100 000 were chosen to participate in our survey.⁴ Telephone contact was made in the spring of 1987 by one of us (K.S.E.) with the office of each pediatric department's chairperson to determine the name of the individual in charge of lead screening in the outpatient department. A program was not included in the study if contact with that individual was not established after three attempts. After we explained the survey by telephone and the contact person agreed to participate, the survey was mailed. Participants were guaranteed personal and program anonymity. A second mailing was sent to nonresponders.

The survey consisted of 15 multiple-choice or short-answer questions concerning protocols for lead screening and characteristics of the population served. Table 2 shows the questions in an abbreviated form. Respondents were asked to estimate numbers or percentages when an actual number or percentage was not available, and they were asked to note when a response was only an estimate.

Table 2.—Abbreviated Summary of Questionnaire Items

1. Characterize the program as urban, suburban, or rural
2. What proportions of Hispanic, black, white, or other groups are served by the program?
3. What are the proportions of payment method for visits (self-pay, private insurance, medical assistance)?
4. What is the initial lead screening test used?
5. Is the initial screening step standardized?
6. What is the upper limit of normal levels for free erythrocyte protoporphyrin, zpp, and lead?
7. At what age are children first screened?
8. How frequently are children screened?
9. What percentage of children seen for well-child care are being screened?
10. Are results of capillary free erythrocyte protoporphyrin determinations available prior to the child's departure from the clinic?
11. Who is responsible for the follow-up of children with abnormal screening test results?

ANALYSIS

We developed criteria to evaluate the screening programs based in part on current official screening guidelines. Criteria taken directly from the guidelines were a first screening by 12 months of age and screening at least yearly thereafter. Although the official guidelines do not call for centralization of screening results and follow-up, the need for such a system is obvious and we included it as the third criterion. Screening programs meeting all three criteria were judged to be adequate.

RESULTS

Twenty-two (78%) of the 28 surveys were returned completed. All 22 programs characterized themselves as urban (rather than suburban or rural). All programs except 1 served populations that were at least 40% minority. At 9 of the programs, 80% or more of the population served were from minority groups. The proportion of the population receiving medical assistance at each center ranged from 40% to 80%.

Programs were scored for the presence or absence of the three criteria

(first screening by 12 months of age, annual screening, and centralization of screening results and follow-up). The results are shown in Table 3. Six programs (27%) met all three criteria and were judged adequate. Four programs (18%) met none of the criteria. The remaining 12 programs (55%) met only one or two of the criteria.

The most frequently met criterion was annual screening, which was done at 16 (72%) of the programs. At 10 of the 22 programs, children were first screened *later* than the recommended age of 12 months, with some programs screening for the first time as late as 18 to 30 months of age. Half of the programs lacked a mechanism within the institution for centralization of collection and interpretation of screening results and for arranging a follow-up of abnormal test results.

Three of the four programs that met none of the criteria were the only three programs to indicate that there was no institutional protocol for lead screening, and that each practitioner followed his or her own protocol for screening, inter-

Table 3.—Program Criteria*

Program	First Screening by Age 12 mo	Children Screened at Least Annually	Centralization
A	+	+	+
B	+	+	+
C	+	+	+
D	+	+	+
E	+	+	+
F	+	+	+
G	—	+	+
H	—	+	+
I	—	+	+
J	+	+	—
K	+	+	—
L	+	+	—
M	+	+	—
N	+	+	—
O	+	+	—
P	—	—	+
Q	—	—	+
R	—	+	—
S	—	—	—
T	—	—	—
U	—	—	—
V	—	—	—

*Plus sign indicates yes; minus sign, no.

pretation, and follow-up of results. All other institutions reported that a specific protocol was provided for the use of all practitioners.

Half of the programs stated that 90% or more of the population served were being screened. Five of the programs did not provide information on the extent of screening. Of the 6 programs reporting less than 90% screening, 2 served populations in which fewer than 50% used medical assistance and fewer than 50% were from minority groups. Of the 17 programs that provided a percentage of the population screened, all but 3 provided estimates. The 3 programs providing actual percentages obtained them by routine institutional review of patient care, either by review of medical records or by review of computer-stored patient data.

Venipuncture was reported as the primary method of obtaining screening specimens by seven (32%) of the programs. Seven programs reported never using fingerstick capillary methods to obtain initial screening specimens. Fifteen programs used a fingerstick as either the primary or alternate method of obtaining screening specimens. Only five (23%) of the programs could obtain an FEP result prior to a child's departure from the clinic.

When asked to indicate the upper limit of acceptable FEP for screening purposes, two directors provided incorrectly high values (60 and 50 $\mu\text{g/dL}$) instead of the recommended value of 35 $\mu\text{g/dL}$. Only three of the programs routinely reviewed their own lead screening practices. Two programs did this by periodically reviewing a number of charts. One program used information from a computerized database of patient records.

COMMENT

Official lead screening guidelines leave much latitude for determining which children to screen. It seems appropriate, in light of the increasing evidence of the deleterious effect of even low-level lead exposure, that the strict-

est interpretation should apply to the screening of high-risk, low-income, inner-city children being served by the programs surveyed.

When we applied our strict set of criteria to screening practices at urban pediatric teaching programs, only 27% met all three criteria. Forty-five percent of the programs reported the initiation of lead screening after the age of 12 months. This practice leaves children unscreened at the age of highest risk for the deleterious effects of undue lead exposure. The lack of central coordination of screening data and follow-up at 50% of the programs weakens the important link between testing and abatement and treatment.

While we were unable to investigate an association between program characteristics and screening adequacy using our data, we were able to determine the frequency of certain practices that are likely to decrease the adequacy of screening.

The lack of institutional guidelines for lead screening was reported by three of the four programs that met none of the criteria for adequate screening. All other institutions stated that a protocol was provided to its practitioners.

The use of venipuncture specimens for screening probably limits the number of children screened because of the extra time required for venipuncture, a reluctance to subject children to venipuncture, and, in some instances, the requirement that the specimen be obtained by the pediatric practitioner. In our experience, the changeover from screening using venous specimens obtained by physicians to using FEP determinations on capillary samples obtained by a trained technician was accompanied by a dramatic increase in the number of children screened. (K.S.E. and B.W.C.F., unpublished data, 1987). Hematofluorometers may be purchased for approximately \$5000, are easily operated, and specimens to be used as controls may be purchased from the distributor.

The ability to obtain the results of a capillary sample FEP prior to discharging the child from the clinic lends several obvious advantages to a screen program. It obviates the need for venous samples in children with a normal FEP value. It allows venous samples to be drawn immediately on all children with elevated FEP values, therefore eliminating the need for often difficult to arrange return visit phlebotomy.

The limitations of this study include the fact that the characteristics of a screening program were obtained by questioning the head of the program rather than by an actual review of program practices. Because most programs had not reviewed their own screening practices, the directors' responses might not reflect actual practices.

It is likely that lead screening guidelines will be reviewed in the near future to attempt to increase the likelihood of detecting and intervening in even low lead exposure cases. Our study indicates that the current guidelines are frequently not being met even at teaching institutions. It is time for each institution providing well-child care to review its lead screening practices and to prepare for a more intensified effort to detect undue lead exposure.

We thank the program directors who participated in this study and shared their suggestions for improvement of screening programs and M. Harris for preparing the manuscript.

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Regulation of Oxygen Concentration Delivered to Infants Via Nasal Cannulas

Nestor E. Vain, MD; Luis M. Prudent, MD; Deborah P. Stevens, RRT;
Margaret M. Weeter, RRT; M. Jeffrey Maisels, MB, BCh

• The administration of oxygen to infants via nasal cannulas is now a common practice in neonatal units although the inspired oxygen concentration reaching the patient's airway is unknown. We measured the hypopharyngeal oxygen concentration in 10 infants who were receiving oxygen via nasal cannulas and assessed the impact of changes in the flow rate and inspired oxygen concentration. Weaning these infants by reducing the flow rate, even if changes are slight, produces clinically important changes in the oxygen concentration reaching the airway. Such changes are poorly tolerated by infants with chronic lung disease. Changing the flow rate and inspired oxygen concentration, rather than the flow rate alone, provides greater precision and is likely to avoid excessive and abrupt changes in the oxygen concentration reaching the airway.

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Oxygen is commonly delivered via nasal cannulas to infants with prolonged oxygen requirements. This practice has simplified nursing care considerably and facilitated early discharge of these infants, permitting the administration of supplemental oxygen at home.¹⁻⁴ This technique makes it difficult, however, to determine the actual fraction of inspired oxygen concentration (F_{IO_2}). Knowledge of the required F_{IO_2} may be important to assess the

clinical course and the response to therapy (eg, diuretics), particularly when planning discharge from the hospital.

To control the F_{IO_2} , most clinicians vary the flow rate through the nasal cannula, while the oxygen source is kept constant.⁵ As the infant breathes, however, air enters from the mouth and around the nasal cannula, and the actual oxygen concentration reaching the airway is unknown.

Since the hypopharyngeal oxygen concentration (F_{Ho_2}) is virtually identical to the tracheal oxygen concentration,^{6,7} we decided to perform direct determinations of the oxygen concentration reaching the patient's airway by measuring the F_{Ho_2} at various flow rates. Our purpose was to provide guidance for physicians who administer oxygen through nasal cannulas and to assess oxygen delivery during weaning.

PATIENTS AND METHODS

We studied 10 infants in clinically stable condition who were receiving oxygen via nasal cannulas. The clinical characteristics of the infants are listed in the Table. The median birth weight was 1290 g (range, 825 to 4090 g), and the median weight at the time of the study was 2130 g (range, 1780 to 4090 g). The median gestational age at birth was 29 weeks (range, 25 to 39 weeks), and the median postnatal age at the time of the study was 52.5 days (range, 19 to 123 days). With one exception, all patients had received mechanical ventilation (median duration of assisted ventilation, 32 days; range, 0 to 75 days).

We monitored the heart rate, respiratory rate, transcutaneous oxygen tension ($TcPo_2$) (Novamatrix, Wallingford, Conn), and oxygen saturation (by pulse oximetry, Biox 3700 Pulse Oxymeter, Ohmeda, Boulder, Colo) throughout the study. Oxygen was delivered to the infants via nasal cannulas (infant Nasal Cannulas 1601, Salter Laboratories, Arvin, Calif), and we sampled the F_{Ho_2} by using a modification of the nasal

oxygen sampler (Fig 1).⁸ We measured oxygen concentrations with a polarographic oxygen analyzer. The $TcPo_2$ electrode was calibrated with a zero solution and room air according to the manufacturer's directions.

A 12F suction catheter was introduced through the infant's mouth into the hypopharynx. The depth of insertion was equal to the distance from the mouth to the earlobe. The catheter was secured with tape, and samples were drawn with the infants at rest when the vital signs, $TcPo_2$, and oxygen saturation were stable. Measurements of the F_{Ho_2} were obtained by drawing the gas samples slowly into the syringe during a period of 60 to 90 seconds. Samples were obtained throughout various respiratory cycles (inspiration and expiration), and sampling continued until the oxygen analyzer readings remained stable. The desired F_{IO_2} was obtained by using a flow oxygen blender (Bird HI/LO). The F_{IO_2} was measured before each hypopharyngeal sampling via a three-way stopcock that was placed in line between the flowmeter and the nasal cannula. The flow rate was selected at the blender's low-flow outlet by using a pressure-compensated flowmeter (Timeter 0-3 Flowmeter, Timeter Instrument Corp, Lancaster, Pa). The accuracy of the flowmeter was evaluated by measuring the actual flow with a calibration analyzer (Timeter RT 200).

By using a Latin square design, infants were assigned randomly to various gas flow rates (0.25, 0.50, 0.75, and 1.0 L/min) and oxygen concentrations (100%, 80%, 60%, and 40%). Readings were obtained when the $TcPo_2$ and oxygen saturation readings were stable (3 to 5 minutes after a change in settings). Each patient was studied with each combination of flow rate and F_{IO_2} as long as the $TcPo_2$ and oxygen saturations were maintained within acceptable limits ($TcPo_2$, 40 to 80 mm Hg; oxygen saturation, 85% to 97%). The flow rate and/or F_{IO_2} were adjusted when these limits were exceeded. Thus, not every patient was exposed to each F_{IO_2} /flow rate combination (Fig 2). The protocol was approved by our Clinical Investigation Committee, and parental consent was ob-

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tained for each study. Analysis of variance was used to determine the effect of changes in the flow rate and blender setting on the $F_{H_{O_2}}$.

RESULTS

The results are shown in Fig 2. For each blender setting and flow rate, the differences in the $F_{H_{O_2}}$ were significant ($P < .001$). We measured the $F_{H_{O_2}}$ in five infants who were breathing room air at flow rates of 0.25 to 1.0 L/min. In all cases, the $F_{H_{O_2}}$ ranged from 0.16 to 0.18. We also determined the $F_{H_{O_2}}$ (without modifying the flowmeter or blender settings) in five patients who cried during part of the study period. The $F_{H_{O_2}}$ decreased during crying by $17.7\% \pm 5.4\%$ (mean \pm SD) from baseline values, and subsequently, it increased when the infant stopped crying. These changes were followed by similar changes in the $TcPO_2$ and oxygen saturation.

COMMENT

Since the tracheal oxygen concentration is almost identical to the $F_{H_{O_2}}$,^{6,7} and arterial oxygenation correlates more closely with the $F_{H_{O_2}}$ than with the settings of the gas delivery systems,⁷ we thought it important to document the actual oxygen requirements (by measuring the $F_{H_{O_2}}$) to monitor the severity of the pulmonary disease.

By using a similar method in adults, Schacter et al⁷ reported that the $F_{H_{O_2}}$ decreases at higher respiratory rates and with mouth breathing. We did not analyze respiratory patterns, but we observed an average decrease in the $F_{H_{O_2}}$ of 17.7% when infants cried and a subsequent increase when they stopped crying. These changes in the $F_{H_{O_2}}$ were followed by similar changes in the $TcPO_2$ and oxygen saturation. When infants breathed room air at various flow rates, the $F_{H_{O_2}}$ was 0.16 to 0.18 in all cases, indicating mixing between inspired and expired gases.

Fan and Voyles⁶ used an indirect method to calculate the oxygen requirements of these patients. They administered 100% oxygen via a nasal cannula and adjusted the flow rate to obtain a $TcPO_2$ similar to that obtained when a known F_{IO_2} was administered via an oxygen hood. By using their recommendations to calculate the oxygen flow when

Clinical Characteristics of Infants Studied

Patient	Diagnosis*	Days Receiving Assisted Ventilation	Gestational Age, wk	Postnatal Age, d	Birth Weight, g	Study Weight, g
1	HMD, BPD	9	33	19	1980	1800
2	Aspiration pneumonia, BPD	0	30	24	1380	2145
3	HMD, PIE, BPD	51	25	62	860	1780
4	HMD, BPD	44	27.5	68	870	2120
5	HMD, BPD	24	31	40	1490	2070
6	HMD, PDA, BPD	32	28.5	54	1200	1900
7	HMD, BPD	32	31	51	1590	2380
8	HMD, PDA, BPD	46	28	87	1040	2335
9	HMD, BPD	75	25	123	825	3620
10	PPH, pneumothorax, BPD	18	39	31	4040	4090

*HMD indicates hyaline membrane disease; BPD, bronchopulmonary dysplasia; PIE, pulmonary interstitial emphysema; PDA, patent ductus arteriosus; and PPH, persistent pulmonary hypertension.

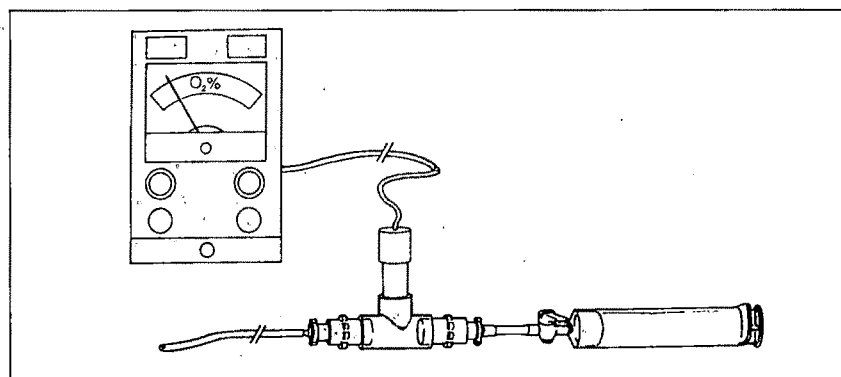
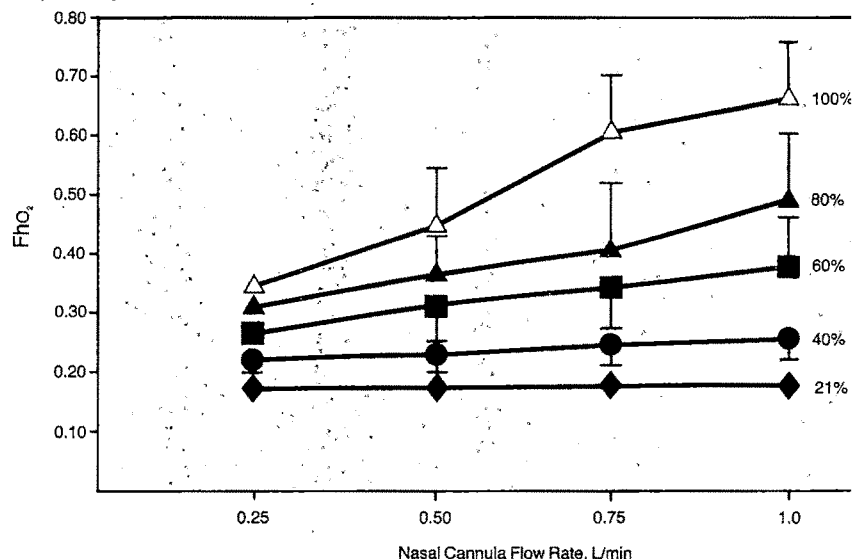


Fig 1.—Hypopharyngeal oxygen (O_2) sampler. A rubber ring was used to fit the analyzer probe securely to the Bird T piece that was connected to a 12F suction catheter and a 60-mL syringe via 15-mm adapters and endotracheal tube adapters. The system was made airtight by sealing the plastic adapters with ethylene dichloride cement.

Fig 2.—Hypopharyngeal oxygen concentration ($F_{H_{O_2}}$) by flow rate and inspired oxygen concentration. Seven to nine measurements were obtained at each setting, with the exception of 0. and 0.25 L/min at an inspired oxygen concentration of 40% where six and five measurements respectively, were obtained.



switching an infant from an oxygen hood to a nasal cannula, we frequently found TePO_2 values to be higher than predicted. The patients who were studied by Fan and Voyles,⁶ however, were significantly larger than ours (mean weight, 3155 vs 2130 g, respectively), and five of their infants weighed more than 3500 g. Because smaller infants have a small inspiratory flow and minute ventilation, they entrain less room air, and the oxygen concentration reaching the airway is likely to be greater. By using regression analysis, however, we did not find a significant inverse relationship between the Fho_2 and weight when the flow remained constant.

Infants in stable condition with chronic lung disease are frequently switched from an oxygen hood to nasal cannulas. Subsequently, weaning is performed by lowering the flow rate, usually in 0.125- to 0.25-L/min decrements. Figure 2 shows that a decrease in the flow rate from 0.75 to 0.50 L/min, at an FIO_2 of 1.0, represents a drop in the Fho_2 from 0.60 to 0.44. Similarly, discontinuing oxygen therapy from a previous flow rate of 0.25 L/min, at an FIO_2 of 1.0, decreases the Fho_2 from 0.34 to 0.17 or to 0.18. It is not unusual to observe a large drop in a patient's TePO_2 or oxygen saturation when oxygen is discontinued in this manner. Changes of this magnitude are poorly tolerated by

infants with bronchopulmonary dysplasia and are seldom attempted in infants who receive oxygen via hoods.

Flowmeters that are capable of delivering lower rates (0.125 L/min) might be more useful for these patients but were not available in our unit at the time of this study. However, Fig 2 shows that decreasing the flow from 1.0 to 0.25 L/min at an FIO_2 of 1 results in a drop of approximately 30% in Fho_2 . Assuming a linear relationship, a decrease of 0.125 L/min would lower the Fho_2 by approximately 5%, an unacceptably large change in clinical practice.

Although our data suggest that greater precision can be achieved by modifying both the FIO_2 and flow rate during the process of weaning, inspection of Fig 2 indicates that reducing the FIO_2 below 60% has little utility because of the minimal change in the Fho_2 that occurs with a change in the flow. As a practical guideline, it appears that weaning should be initiated at an FIO_2 of 100% by decreasing the flow rate from 1.0 to 0.25 L/min. For the next step, the flow rate should be returned to 0.75 L/min at an FIO_2 of 80%, followed by a decrease in the flow rate to 0.25 L/min. The same sequence can be applied at an FIO_2 of 60%. There does not appear to be any advantage in decreasing FIO_2 concentrations below 60%, and once this level has been reached, a decrease in the

flow rate alone is the preferred course of action.

Although our method for measuring the Fho_2 is simple, it is not practical for everyday clinical use. The data in Fig 2 can be used, however, to provide an estimate of the appropriate flow rate and FIO_2 . The SDs show that a considerable individual variation in the Fho_2 may, nevertheless, occur, and independent verification of blood oxygenation is necessary at appropriate intervals. The application of this technique should, therefore, be limited to well-controlled inpatient settings.

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Congenital Cardiovascular Malformations in Twins and Triplets From a Population-Based Study

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• Data from the Baltimore-Washington Infant Study of congenital cardiovascular malformations permitted detailed analysis of congenital cardiovascular malformations in 62 twins and 3 triplets and 2303 singleton cases. A probability sample of controls ($n = 2793$) included 43 twins. The case prevalence of multiple births was 28 of 1000, compared with a 15 of 1000 prevalence among controls ($\chi^2 = 5.7$). There were more girls among case twins than among case singletons and controls ($\chi^2 = 9.0$). Monozygosity was no more frequent in case twins than in controls. Looping defects occurred in 4 monozygotic twin pairs compared with only 1 dizygotic twin pair. The twinning process itself may be implicated in the development of congenital cardiovascular malformations in some of these infants, especially those with looping defects, but concordance of types of defects in 4 of 65 pairs implicates genetic factors in the determination of some forms of congenital cardiovascular malformations.

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Human twins are a unique resource for evaluating genetic and environmental contributions to the etiology of birth defects such as congenital cardiovascular malformations (CCVM). Although familial aggregation has been demonstrated consistently for CCVM,¹ studies of twins with this common group of birth defects have failed to confirm a significant genetic component.²⁻⁴ Clinical and epidemiological studies of CCVM have reported an increased frequency of these malformations among same-sex twins.^{3,5-7} The cause of this apparent excess has been attributed to the potentially teratogenic effect of the monozygotic twinning process itself.⁸

An accurate estimation of the preva-

lence and determination of types of CCVM among twins compared with those among singletons has not yet been achieved. Data available on multiple births from the Baltimore-Washington Infant Study (BWIS), a population-based case-control study of CCVM, permit a detailed descriptive analysis of heart defects in multiple births compared with heart defects in singletons. We were thus able to address the following issues: (1) prevalence of CCVM in twins compared with prevalence in singletons; (2) the frequency of monozygosity and dizygosity among affected twins; (3) the sex ratio of case twins, compared with sex ratio of case singletons; (4) concordance for CCVM among pairs of monozygotic twins and dizygotic twins; and (5) evidence of genetic factors contributing to CCVM.

METHODS

Data for this study came from all infants enrolled in the BWIS between January 1981 and December 1986. The BWIS is an ongoing case-control study of the resident birth cohort of the State of Maryland, the District of Columbia, and six counties in Northern Virginia, an area of approximately 90 000 annual births.⁹ Virtually complete ascertainment of all liveborn infants in the first year of life with confirmed CCVM is achieved through multiple case sources including 6 pediatric cardiology centers and 52 collaborating hospitals. A systematic review of autopsy logbooks at community hospitals, together with an annual review of death certificates, ascertains unreferred cases.¹⁰

Cases are defined as infants less than 1 year old with structural cardiac abnormalities confirmed by echocardiography, cardiac catheterization, surgery, or autopsy. Patent ductus arteriosus in premature infants (gestational age, <38 weeks) is excluded. Control infants had, by definition, no cardiac defects. A probability sample of control infants was selected by computer algorithm to be representative of the birth cohort within area hospitals.¹⁰ Strict confidentiality is maintained for all data gathered from human subjects, and the BWIS has institutional Human Subjects Review Board approval.

When multiple members of a twin or trip-

let set have CCVM, only the firstborn infant is considered a "case." Zygosity is determined chiefly by the mothers' reports, since information regarding placentation or serological markers is usually unavailable.

Congenital cardiovascular malformations were classified into embryonic mechanistic groups using the system of Clark¹¹: (1) truncal malformations, such as tetralogy of Fallot; (2) hemodynamic abnormalities, such as perimembranous ventricular septal defect; (3) extracellular matrix abnormalities such as atrioventricular canal; (4) excessive cellular death, such as Ebstein's anomaly; and a group of as yet unverified categories (5a) looping abnormalities, such as levocardia; (5b) targeted growth abnormalities such as total anomalous pulmonary venous return; (5c) and other defects, such as pulmonary vein stenosis. The advantage of this classification system is that it permits aggregation of seemingly diverse anatomic defects into groups that are hypothesized to be developmentally related.

RESULTS

From 1981 to 1986, 62 case twins (of whom 2 pairs were conjoined) and 3 case triplets were included among the 2303 case infants whose parents were interviewed in the BWIS. In this analysis conjoined twin pairs were classified as case twin and 1 cotwin. Among 2793 control infants, there were 43 infants from multiple gestations, none of whom was conjoined or a triplet.

Cases were almost twice as likely as controls to be from a multiple birth (2.8% of cases and 1.5% of controls; $P < .03$, Table 1). However, the distribution of zygosity was very similar among case infants (33.9% were monozygotic) and control infants (27.9% were monozygotic), with no significant excess of monozygosity observed in case ($\chi^2 = 0.413$). There were significantly more girls than boys in the case group compared with twins in the control group ($\chi^2 = 9.0$, $P < .005$, Table 1), while the ratio of male to female infants among case singletons was equal to that among controls.

Some types of CCVM, such as aort

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Table 1.—A Comparison of the Proportion of Twins Among Cases and Controls*

	Cases (%)† (n = 2303)	Controls (%)‡ (n = 2793)
Twins	65 (2.8)	43 (1.5)
Singletons	2238 (97.2)	2750 (98.5)

* $\chi^2 = 5.72$, $P < .03$.

†Proportion of males in twins was 29.2%, in singletons 51.0%.

‡Proportion of males in twins was 58.1%, in singletons 50.2%.

Table 2.—Congenital Cardiovascular Malformations in Male and Female Multiple Births by Mechanistic Group and Specific Lesion

Mechanistic Group of Defects	Male Female	
	Male	Female
1 Conotruncal		
Tetralogy of Fallot	1	3
Dextrotransposition of the great arteries	0	2
2 Hemodynamic		
Secundum atrial septal defect	5	0
Coarctation of the aorta	0	3
Perimembranous ventricular septal defect	4	11
Aortic valve stenosis	2	4
Pulmonary valve stenosis	2	5
Bicuspid aortic valve	1	0
Hypoplastic left heart syndrome	0	1
Patent ductus arteriosus	0	1
Pulmonary atresia	0	1
Double aortic arch	0	1
3 Extracellular matrix		
Atrioventricular canal	2	4
4 Cellular death		
Muscular ventricular septal defect	0	2
Ebstein's anomaly	0	1
5 Unconfirmed categories		
a Looping	2	3
b Targeted growth		
Total anomalous pulmonary venous return	0	1
c Miscellaneous		
Pulmonary vein atresia	0	1
Pulmonary vein stenosis	0	1
Cardiomyopathy	0	1

valve stenosis, secundum atrial septal defect, and coarctation of the aorta, have been reported to have altered sex ratios,¹² but among BWIS twins these alterations in sex ratio were not observed (Table 2). Aortic valve stenosis, reportedly more common in boys, was found in four twin girls and two twin boys; coarctation of the aorta, also usually more common in boys, was found in three twin girls but no twin boys. Con-

Table 3.—Congenital Cardiovascular Malformations in Twins and Singletons

Mechanistic Group of Defects	Twins, No. (%)*				Singletons, No. (%)
	MZ	DZ	UZ	Total	
Conotruncal	2	4	1	7 (10.8)	399 (17.8)
Hemodynamic	12	27	1	40 (61.5)	1332 (59.5)
Extracellular matrix	2	3	1	6 (9.2)	195 (8.7)
Cellular death	2	1	0	3 (4.6)	81 (3.6)
Looping	4	1	0	5 (7.7)	88 (3.9)
Targeted growth	0	1	0	1 (1.5)	56 (2.5)
Miscellaneous	0	3	0	3 (4.6)	87 (3.9)

*MZ denotes monozygotic; DZ, dizygotic; and UZ, unknown zygosity.

versely, secundum atrial septal defect, with a reported excess in girls, was diagnosed in five twin boys but no twin girls.

The types of CCVM noted in twins and singletons are compared in Table 3. Conotruncal and targeted growth defects were slightly less common in twins than in singletons, although the small number of twins with these defects made rigorous statistical comparison problematic. With the exception of the slight, but not significant, increase in the looping defect category among twins compared with singletons, the other groups were similar in proportions. Looping defects occurred in 4 (18.2%) of 22 monozygotic twins, but only 1 (2.5%) of 40 dizygotic twins.

Among the nonconjoined twins, 4 case twins had a cotwin with CCVM. Of the 20 pairs of monozygotic nonconjoined twins, there were 2 pairs (10%) of twins in which both members of the pair were affected. In 1 pair, both had secundum atrial septal defect, while in the other, 1 twin had pulmonary valve stenosis and 1 had perimembranous ventricular septal defect. Of the 40 dizygotic twin and triplet sets, 2 (2.5%) had affected cotwins. One set of triplets had 2 affected members, 1 with bicuspid aortic valve and the other with hypoplastic left heart syndrome. In addition, both members of a pair of twins of unknown zygosity had atrioventricular canal. Each of the affected twin sets were concordant for mechanistic group, but not necessarily for specific anatomical defect.

Extracardiac anomalies occurred in 15 case twins (23.1%) and in none of the control twins in the BWIS. Cytogenetic anomalies were not reported in any of

the monozygotic case twins and in only 3 of the dizygotic case twins (trisomies 13, 18, and 21). Among case twins with non-cytogenetic extracardiac anomalies, 2 monozygotic twins had umbilical hernias, and 1 had a diaphragmatic hernia. The 2 pairs of conjoined twins had multiple malformations. Two dizygotic case twins had omphaloceles, 1 had pectus excavatum, 1 had aniridia, 1 had microcephaly, and 1 had VATER association. One case twin of unknown zygosity had a limb reduction defect, a cleft palate, and an absent humerus.

COMMENT

The BWIS attempts to achieve complete ascertainment of all confirmed CCVM in the resident birth cohort including CCVM in multiple gestations. Diagnostic criteria are deliberately strict to prevent inclusion of potentially innocent murmurs detected only by auscultation and otherwise unconfirmed. Although previous studies have suggested a higher prevalence of CCVM, there is agreement that the prevalence of confirmed CCVM is approximately 4 per 1000 among liveborn infants under 1 year of age.¹³

In the BWIS, there was an excess of case twins compared with control twins. An association between multiple births and CCVM has been observed by others in epidemiological studies of birth defects using both prospective and retrospective methods.^{3,7} Twinning itself may contribute to the development of cardiac defects if the presence of two embryos developing in the same uterus alters the "biological clock" of one or both.¹⁴

In the BWIS, the distribution of zygosity was similar in multiple gestations

in cases and controls. In contrast to previous studies in which an excess of monozygotic twins has been reported,^{3,6} results from some of these earlier series may have reflected ascertainment bias for monozygotic twins, or lack of systematic diagnosis of heart defects. In our study, zygosity information was available only through mothers' reports rather than by examination of the placentas or serological markers. The latter two methods are preferable, but when these methods have not been used, the questionnaire method of zygosity determination has been employed with nearly comparable results.¹⁵

More female case twins were reported in the BWIS, a finding also noted by Anderson.² The reason for an excess of twin girls among liveborn cases of cardiac malformation is difficult to determine, since female singletons with CCVM are not overrepresented. In an unselected series of spontaneously aborted twins with and without heart defects, female twin pairs were more likely to be aborted earlier in gestation, while male twin pairs were more frequently aborted toward the end of the pregnancy.¹⁶ This suggests differential survival of female twins who, if not aborted early, may be more likely to be born alive even with a heart defect. Measurement of differential survival was not possible using data from the BWIS, which ascertains only liveborn infants. Carefully designed fetal echocardiography studies may help to resolve questions about both the apparently altered sex ratio in twins with CCVM and the incidence of CCVM in

twins compared with singletons.

Looping abnormalities accounted for almost twice the proportion of twins compared with the proportion of singletons (7.7% and 3.9%, respectively), and were also more frequently reported in monozygotic than in dizygotic twins. Looping abnormalities may represent disturbances of laterality. Burn and Corney⁶ attributed the excess of same-sex twins to defects related to cleavage of the single zygote, and they suggested that a disturbance of laterality should be more common in monozygotic twins.

The lack of concordance in monozygotic twins has been used as evidence that there is little or no genetic contribution to the etiology of heart defects.⁷ The results of this twin analysis of population-based case-control data did not directly support that conclusion, as 10% of the monozygotic but only 2.5% of the dizygotic cases had affected cotwins. The use of a classification system of heart defects that permits grouping of lesions by presumed pathogenic mechanism has proved useful in studying the familial recurrence of CCVM in human families¹ and may be equally useful in evaluating concordance in twins since it highlights similarities that may be overlooked when an anatomic classification system is used.

The proportion and type of extracardiac anomalies were different in case twins compared with case singletons and with controls. Bearing in mind that the numbers are small, there were relatively few cytogenetic anomalies in case twins compared with case singletons.¹⁷ This may be due to selection, since aneuploidy is associated with a very high

spontaneous abortion rate.¹⁸ Aneuploidy and a heart defect may be relatively incompatible with survival to live birth. Noncytogenetic extracardiac anomalies were relatively common in case twins. This may reflect a teratogenic effect of twinning itself, since none of the case twins with extracardiac anomalies had similarly affected cotwins.

In summary, we found that (1) heart defects occurred in excess among multiple gestations, but the distribution of zygosity was not different among cases with CCVM compared with controls; (2) looping abnormalities appeared to be increased; and (3) among twin pairs, only 6.2% had a cotwin with CCVM, but the defects were concordant by mechanistic group.

These findings lead us to speculate that the twinning process may be related or contributory to the development of CCVM, particularly looping and conotruncal defects. This process would not be expected to affect both members of a twin pair equally. This may account for the large proportion of discordant twin pairs. However, since all sets in which multiple members were affected showed concordance for mechanistic group, the suggestion remains that development of cardiac defects at some level may be under genetic control.

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Nonphenylketonuric Hyperphenylalaninemia

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• Sixteen subjects with nonphenylketonuric hyperphenylalaninemia were followed up during a period of years. Dietary treatment did not seem to influence the outcome, and no relationship between blood phenylalanine and intellectual outcome was demonstrable.

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It was some years after phenylketonuria (PKU) was described by Fölling,¹ that clinicians became aware of milder forms of hyperphenylalaninemia. Terminology for the various degrees of hyperphenylalaninemia was confusing.² In addition, it was unclear what levels of phenylalanine required dietary treatment.³

In an attempt to elucidate the long-term outcome of children with milder forms of hyperphenylalaninemia, it was decided to follow up all patients more than 5 years old with non-PKU hyperphenylalaninemia, seen at the Childrens Hospital of Los Angeles since 1957. It was possible to locate 20 such children, some of whom were treated for a time with a phenylalanine-restricted diet while others were not. Often treatment with the phenylalanine-restricted diet was instituted because the index case was thought initially to have classic PKU or because the clinician in charge based his or her decision to treat on some arbitrary value such as "over 720" $\mu\text{mol/L}$ or "over 900" $\mu\text{mol/L}$. The major reason for confusion regarding treatment was that good data documenting dietary benefit or lack thereof were not available. The largest published series consisted of 14 chil-

dren⁴ with mild hyperphenylalaninemia seen at the Boston (Mass) Children's Hospital. Thus it was hoped that this review of experience at the Childrens Hospital of Los Angeles would shed additional information on the natural history of children with non-PKU hyperphenylalaninemia.

METHODS

Since 1957, infants and children with all degrees of hyperphenylalaninemia have been referred for evaluation to the PKU Clinic at Childrens Hospital of Los Angeles. Twenty children met the following criteria and were included in our study:

1. phenylalanine blood levels, on a normal diet, between 240 and 1199 $\mu\text{mol/L}$ and normal bipterin studies in urine.
2. a typical response on a natural protein challenge of 180 mg/kg per day of phenylalanine for 3 days with blood phenylalanine levels less than 1200 $\mu\text{mol/L}$ and absent-to-little excretion of organic acids in the urine.
3. identification by either newborn screening programs or sibling testing in affected families.
4. age older than 5 years.

The Wechsler Intelligence Scale for Children-Revised was administered to provide a global index of current intellectual function.⁵ For persons older than 16 years, the Wechsler Adult Intelligence Scale-Revised⁶ was administered. The Bender Visual-Motor Gestalt Test⁷ for children was given to assess perceptual motor function utilizing the Kopitz⁸ scoring system for determining mental age. The Wide Range Achievement Test⁹ was used to measure academic achievement in reading, spelling, and arithmetic, and the Vineland Social Maturity Scale¹⁰ was administered as a measure of social competence. The PKU Collaborative Study Family Evaluation Form measured family stability¹¹ and provided an overall view of family function. Since this is an unstandardized procedure, the Two-Factor Index of Social Position¹² (Hollingshead Scale) provided additional information necessary to evaluate family stability. Due to the small sample size, nonparametric test procedures as well as cluster analysis were employed. Spearman Rank Order Correlations and the Mann-Whitney U test were also utilized.

DESCRIPTION OF THE SAMPLE

Four of the 20 families decided not to participate due to travel limitations or time restrictions. Of the remaining 16 patients, 9 were female and 7 male. All were white and averaged 15 years of age, ranging from 5 to 39 years. Nine patients had been on a restricted phenylalanine diet for varying periods. The 2 oldest patients (ages 30 and 39 years) were born prior to availability of treatment. The 5 youngest were untreated because our experience suggested that dietary treatment was unnecessary.

The pregnancy history of the mother of each child was ascertained and found to be normal as was birth weight and early development. Three families had two patients each; thus, there were 13 family cohorts. Two families had a history of hypertension, but there were no major congenital anomalies or other metabolic disease. There was a history of depression in one patient who was treated with the phenylalanine-restricted diet and in one who was not. Another patient received counseling for emotional difficulties in school and yet another required academic tutoring while attending regular school. Except for these four patients, all others appeared to be remarkably free of extraneous factors that might have altered normal development. One patient had been slightly premature, weighing 2200 g and measuring 43 cm in length at birth.

RESULTS

We identified two clusters: one treated and the other untreated. The first group consisted of 9 patients who had received a phenylalanine-restricted diet for an average of 4 years 3 months (range, 1 to 9 years). None of these were on dietary restriction at the time of assessment for this study. Among the treated patients the mean IQ was 98.5, compared with an associated maternal mean IQ of 114. Among the 7 untreated patients the mean IQ was 101.6, with an

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associated maternal mean IQ of 106.7. The mean IQ of all 16 patients was 99.9, compared with a maternal mean IQ of 110.8. Due to the small sample size and due to the fact that adults were tested with the Wechsler Adult Intelligence Scale and the children with the Wechsler Intelligence Scale for Children, this difference was not considered significant.

Table 1 delineates blood phenylalanine levels; overall, verbal, and performance IQ scores; Wide Range Achievement scores in reading, spelling, and arithmetic; Bender Koppitz scores; and Vineland Social Maturity results at the time of the study. These data were analyzed by the Spearman Rank Order Correlation. All of the correlations of IQ with current phenylalanine levels were negative, ranging from -0.107 to -0.176 . There was no consistent correlation between blood phenylalanine level and IQ results. Four patients exhibited phenylalanine levels above $900 \mu\text{mol/L}$ at the time of testing; none displayed the usual findings of classic PKU.

Additional analyses were made to investigate the possible beneficial effects of diet therapy on educational achievement or behavior. These data again did not reveal any significant beneficial association between diet therapy and the

assessments utilized in this study, namely the Wechsler Intelligence Scale for Children, Wechsler Adult Intelligence Scale, Wide Range Achievement Test, Bender Gestalt, or the Vineland Social Maturity Scale.

Since the degree of dietary adherence (compliance) and duration of dietary therapy could also be factors¹⁸ that might influence outcome, these two items were also evaluated. Compliance was evaluated by serial phenylalanine levels. Again no significant correlations were found between adherence to diet and/or outcome, or duration of therapy and outcome as measured by IQ, academic achievement, or behavior.

Correlations were also sought between the Hollingshead Two-Factor Indices of Social Position and the results of intelligence and behavior tests (Table 2). In this case the Hollingshead Score was used as an indicator of factors or influences that might enhance the likelihood of dietary compliance. A significant negative correlation was demonstrable between this measure and verbal IQ scores ($P < .02$) and performance IQ scores ($P < .01$). A similar analysis in this group of treated subjects of Hollingshead Indices with Wide Range Achievement Test scores revealed a significant negative correlation with reading ($P < .01$) but not with spell-

ing ($P > .05$) and arithmetic ($P > .05$). A positive correlation was observed between the Bender Gestalt Visual Motor Test and the Hollingshead Scores ($P < .05$). However, a negative correlation was observed between the Vineland Social Maturity Scale and the Hollingshead Scores ($P > .05$). Finally there was no significant correlation between the PKU Collaborative Study Family Evaluation Form and outcome of the treated and untreated patients. These results demonstrate the lack of a consistent relationship between compliance with and duration of dietary therapy and psychoeducational outcome in these patients (Table 2).

COMMENT

The following classification is accepted in most centers treating children for PKU, and is the basis of this report.

Classic PKU refers to individuals with the following: elevated phenylalanine levels generally exceeding $1200 \mu\text{mol/L}$ on a regular diet; excretion of the typical organic acid metabolites of phenylalanine in the urine; and little to no phenylalanine hydroxylase activity in the liver. Without treatment these individuals usually are severely mentally retarded and develop neurological signs and symptoms over a period of months or years.³

Atypical PKU is descriptive of indi-

Table 1.—Phenylalanine Level and Psychometric Test Results*

Patient No./Age, y mo	Wechsler Scales				Wide Range Achievement Test				
	Pheny	IQ	Verbal IQ	Performance IQ	Reading	Spelling	Math	Bender	Vineland
1/9/7	11.5	100	90	112	115	134	98	2	140
2/14/5	12.4	105	103	108	90	117	106	0	125
3/5/2	11.5	85	79	95	76	70	108	15	109
4/16/7	7.1	112	107	112	130	130	155	1	121
5/6/5	10.3	111	114	105	76	8	115	8	127
6/5/2	11.9	80	81	81	71	73	98	18	109
7/5/5	8.3	118	124	105	59	89	93	17	123
8/21/5	13.4	99	104	87	91	114	85	2	116
9/22/0	15.3	99	103	94	111	109	97	0	110
10/30/0	15.1	111	108	114	105	108	114	0	114
11/18/2	17.0	102	95	110	92	90	61	0	112
12/39/0	10.3	79	82	77	63	71	49	0	78
13/17/0	19.4	94	100	89	107	123	63	0	113
14/18/0	5.2	89	89	100	73	68	54	0	100
15/13/0	13.3	109	101	118	93	94	78	1	120
16/7/5	4.4	105	106	104	112	106	108	1	121

*Bender represents Bender-Koppitz scores; Vineland, the Vineland Social Maturity Scale.

Table 2.—Correlation of the Results of Hollingshead Two-Factor Indices of Social Position (Indicator of Stability and Thus Compliance) With Diet Therapy in Variant Hyperphenylalaninemia

	Spearman Rank Order Correlation (Rho)	P
Wechsler Scales		
Verbal	-0.88	<.01
Performance	-0.67	<.01
Total Score	-0.743	<.02
Wide Range Achievement Tests		
Reading	-0.99	<.01
Spelling	-0.62	>.05
Arithmetic	-0.55	>.05
Bender-Gestalt	0.64	<0.05
Vineland Social Maturity Scale	-0.52	>.05

viduals with blood phenylalanine levels of 600 to 1199 $\mu\text{mol/L}$ who usually remain asymptomatic without specific dietary treatment and may not excrete significant amounts of phenylalanine metabolites in their urine. Phenylalanine hydroxylase is significantly decreased in the liver and ranges from a few degrees of activity to as high as 5% to 10% of the normal activity.

Benign persistent hyperphenylalaninemia refers to persons with blood phenylalanine levels of 240 to 599 $\mu\text{mol/L}$ and normal urinary findings that do not require treatment.

The purpose of this investigation was to evaluate the impact of non-PKU hyperphenylalaninemia on the mental and physical health of affected individuals. We also assessed whether a phenylalanine-restricted diet during the early years of life was effective in promoting better psychoeducational achievement. While dietary restriction of phenylalanine is the accepted mode of treatment for classic PKU,¹⁸ the treatment of milder forms of hyperphenylalaninemia has varied considerably in different PKU treatment centers.¹⁴ Our data do not substantiate any beneficial effect of dietary phenylalanine restriction in individuals with non-PKU hyperphenylalaninemia during early childhood, and is in agreement with a much earlier report by Levy et al⁴ in 1971. Furthermore, the data do not indicate any relationship of the level of IQ and psychoeducational achievement with blood levels of phenylalanine. This latter finding may be consistent with the finding by Holtzman et al¹⁵ that there may be a threshold of blood phenylalanine below which intel-

lectual damage does not occur in classic PKU.

While the general physical health of this group of patients has been excellent, two have required help with emotional disorders and one of these has exhibited overt psychosis. His blood phenylalanine levels over a period of several years ranged between 600 and 840 $\mu\text{mol/L}$. Whether this observation is related to hyperphenylalaninemia is open to question and requires additional study. No associated patterns of mental illness in other family members was found.

The findings in this investigation were surprising to us. The lack of any relationship between intellectual achievement and blood phenylalanine levels was unexpected. Twelve of the 16 patients have constantly had blood phenylalanine levels above the recommended treatment ranges for classic PKU and yet did not exhibit any of the problems seen in untreated patients with PKU. Krause et al¹⁶ have reported that even small elevations of blood phenylalanine levels are associated with computerized electroencephalographic changes and slowed reaction time in certain psychoeducational activities. Despite the fact that the blood phenylalanine levels in our patients are significantly higher than those reported by Krause et al, the patients in the present study were found to be progressing well in school and seem normal with regard to intellectual achievement. Our data support the conclusion that there is no evidence to support dietary intervention in the milder forms of hyperphenylalaninemia.

One word of caution, however, is necessary in regard to such patients. The female patients with levels of phenylalanine recorded in Table 1 are at risk for anomalies in their future offspring. There is a significant maternal-to-fetal gradient of 90 to 180 $\mu\text{mol/L}$ for phenylalanine. A maternal level of 720 $\mu\text{mol/L}$ may be as high as 900 $\mu\text{mol/L}$ in the fetus. Therefore, it is imperative to follow up such patients so that pregnancy can be planned in conjunction with a phenylalanine-restricted diet.

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The Adolescent Heterosexual Relationship and Its Association With the Sexual and Contraceptive Behavior of Black Females

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• We tested the hypothesis that the nature of the heterosexual relationship would be associated with the contraceptive and sexual behavior among three groups of females: those with a boyfriend who agreed to be interviewed ($n=31$); those whose boyfriends refused to be interviewed ($n=38$); and those without a single identifiable boyfriend ($n=44$). A pretested questionnaire was administered to a random sample of 113 black females aged 12 to 18 years from a lower socioeconomic population. The three groups did not differ in age, Tanner stage, previous pregnancies, or in demographic variables. Females with boyfriends were more likely than others to be currently sexually active. Overall, 47.8% of the sample was sexually active. Females whose boyfriends were interviewed were more likely to feel that having a baby would ruin their life. Among sexually active females ($n=54$), a higher percentage of females

whose boyfriends were interviewed (90%) were currently using a prescription method of birth control and demonstrated higher previous contraceptive compliance. There were no differences between the groups with boyfriends in the degree that the females felt their boyfriends supported their use of birth control; those without boyfriends perceived less support. Six months after the initial interview, a higher percentage of sexually active females had a boyfriend as compared with other subjects. Although the 31 females and their boyfriends differed in the mean scores of several sexual behavior and attitude scales, the girls' and their boyfriends' scores on these scales were moderately correlated. These findings suggest that the nature of the heterosexual relationship may influence both the sexual and the contraceptive behavior of black female adolescents.

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During the last 2 decades much of the research directed at the problems of adolescent sexuality, contraceptive behavior, and unwed pregnancy has been conducted outside the social context in which these problems normally occur.¹ Instead of examining these behaviors in terms of the dynamics of interpersonal and sexual relationship development, investigators have tended to study various structural, social, psychological, and demographic factors thought to be predictive of premarital coital and contraceptive behavior by evaluating samples of predominantly older adolescent females. Until recently peer and friendship networks were rarely studied, al-

though it was assumed that such relationships were important in adolescent sexual socialization.

Studies from the peer reference group literature have found that as children progress into adolescence, parental influences on sexual behavior tend to decrease and peer reference group influences tend to become increasingly important.^{2,3} These studies have generally found a strong, positive relationship between adolescents' and their peers' sexual attitudes and behaviors.^{4,5} Billy et al⁵ reported that after race and school grade were controlled, males neither influenced one another's sexual behavior nor selected each other as friends on the basis of having or not having sexual intercourse. There was a relationship between the sexual behavior of adolescent females and their friends. In follow-up studies on a separate sample, Billy and Udrez⁶ and Billy et al⁷ found no similarity in sexual behavior between adolescents and their same-sex friends for black males or females. Only white

adolescents established same-sex best friendships based on similarities in sexual behavior.

One unanswered question is: what impact does the adolescent female boyfriend have on her sexual attitude and behavior? As a relationship develops, the girl's boyfriend may evolve into the most significant reference individual in the adolescent female's life with regard to her sexual and contraceptive behavior.^{6,8} This may be especially true for black females, who are influenced less than white males or females by same-sex friends.^{6,7} Although the male partner is very important in the dynamic social process that results in adolescent pregnancy, there is little information regarding the effect of the male partner on sexual and contraceptive behavior. We have previously hypothesized that the establishment of a long-term monogamous relationship will result in changes in both sexual attitudes and behavior.^{8,10} As the length of time of the heterosexual relationship increases, there will be a corresponding increase in the frequency of sexual intercourse and more consistent use of birth control.

The purpose of this study is to describe the sexual and contraceptive behavior of three groups of black female adolescents with different heterosexual relationships. We also describe the similarities and differences in the sexual and contraceptive behavior of the female subjects and their boyfriends.

SUBJECTS AND METHODS

Sample

The Children and Youth Project for the State of Georgia, Augusta, provides comprehensive health care to children and adolescents residing in six low-income housing projects at no cost to the patients. At the time of this study, approximately 400 black female adolescents between the ages of 12 and 18 years were enrolled in the Children and Youth Project

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Using a random numbers table, we selected 125 of the females with the goal of enrolling a minimum of 100 subjects in the study. One hundred fifteen (92%) subjects agreed to participate in the study.

Procedures

After informed consent was obtained, a pretested questionnaire was administered to each girl by one black interviewer with a master's degree in psychology. The interviewer was masked to the purpose of the study. The questionnaire had undergone a 2-week test-retest pretest using 16 black female adolescents from the same population who were not enrolled in the study. The test-retest correlations for the various scales making up the questionnaire ranged from $r = .88$ to $r = .99$, with a mean of $r = .96 \pm .05$.

The questionnaire was divided into two sections. The first section contained demographic data and scales measuring behavior, attitudes, and knowledge concerning sexuality, pregnancy, and contraception.^{3,11-14} This section was administered verbally and scored by the interviewer. The second section contained the Nowicki-Strickland Locus of Control scale (range, 4 to 26),¹⁵ the Coopersmith Self-esteem Inventory (range, 4 to 22),¹⁶ and standardized scales measuring attitudes toward physicians (range, 0 to 7),¹¹ anomia (range, 0 to 5),¹⁷ well-being (range, 1 to 4), and future career and education plans.^{3,11} The second section of the questionnaire was self-administered. Following the completion of the second section of the questionnaire, the girls were shown photographs of females at different Tanner stages and asked to determine their own Tanner stage.¹⁸

Each girl's medical record was reviewed for various events occurring 1 year prior to her entry into the study. Information collected included previous pregnancies and their outcomes, previous contraceptive methods used, changes in methods, reported side effects from methods, noncompliance with or discontinuance of contraceptives, contraceptive failures, and number of family planning visits. These data were used to assess the validity of the girl's responses to similar items on the questionnaire.

After the interview the girl was asked permission to interview her boyfriend. If the girl's boyfriend accompanied her to the clinic, he was asked by his girlfriend to participate in the study at that time. If the female had come to the clinic alone, she was given a 3 × 5-inch card to give to her boyfriend, explaining the study and asking him to call to make an appointment. None of the girls refused permission to have their boyfriends interviewed and all reported that they gave the card to their boyfriend and requested that he participate in the study. Thirty-one of the females had boyfriends who agreed to participate in

the study and be interviewed. Thirty-eight females had one identifiable boyfriend each, but their boyfriends refused to be interviewed. Forty-four females did not have an identifiable boyfriend at the time of the interview. The 31 boyfriends who agreed to be interviewed were administered the same questionnaire as the girls by the same black female interviewer. Based on our interviews with the three groups of females and the boyfriends who agreed to be interviewed, we hypothesized that the heterosexual relationships of these three groups of black female adolescents were distinctly different from one another. This assumption directed the remaining data analysis.

Six months after the initial interview, 118 (98.3%) of the 115 girls were administered a second questionnaire assessing whether any changes had occurred in their sexual and contraceptive behavior during the 6-month period. Two girls could not be contacted for this interview. Data collected included changes in the female's relationship with her boyfriend, pregnancy and outcome of the pregnancy, contraceptive methods used and any changes in methods, noncompliance with birth control, and number of times she had engaged in coitus without using birth control. The boyfriends were not interviewed again at this time.

Statistical Analysis

Data from the total sample ($n = 113$) were analyzed with χ^2 , analysis of variance (ANOVA) tests, Kruskal-Wallis analysis of variance tests, and Tukey multiple comparison tests. Interval data are presented as mean \pm SD. Statistical significance was considered $P \leq .05$. Mean differences in sexual attitudes and behavior between the 31 females and their boyfriends were tested with paired t tests. Although the differences between the 31 girls and their boyfriends could be tested with either t tests for two independent means or Kruskal-Wallis ANOVA, paired t tests were chosen to provide a conservative test of the hypothesis. Correlations between demo-

graphic, sexual behavior and attitudes, and sociopsychological variables measured on the 31 girls and their boyfriends were computed using Pearson's r and Kendall's τ correlation coefficients.

RESULTS

The three groups of females did not differ ($P > .05$) in age, education, postmenarchial age, or in any demographic variables (Table 1). However, the three groups of females differed significantly ($P \leq .005$) in their sexual behavior (Table 2). Although the two groups of subjects with boyfriends did not differ in the percentage who had ever been sexually active, both groups had higher rates of previous sexual activity than the group of females with no boyfriend. Only 25% of the subjects with no current boyfriend had ever engaged in coitus. Even though the two groups of subjects with boyfriends did not differ in the mean number of months they had been dating (Table 1), a significantly higher percentage of the girls whose boyfriends agreed to be interviewed were currently sexually active than the females whose boyfriends refused to be interviewed (Table 2). These findings support the assumption that these three groups of females differed in their heterosexual relationships.

The females whose boyfriends were interviewed and those without boyfriends had stronger negative feelings ($P \leq .0118$) about the possibility of having a baby than the girls whose boyfriends refused to be interviewed (Table 3). The three groups did not differ in the other scales measuring attitudes and knowledge concerning birth control or pregnancy.

Females without a boyfriend had sig-

Table 1.—Means \pm SD of Variables From the Initial Questionnaire*

	Boyfriend Interviewed (Mean \pm SD)	Boyfriend Refused Interview (Mean \pm SD)	No Boyfriend (Mean \pm SD)
Age, y	15.2 \pm 1.8	15.2 \pm 1.9	14.4 \pm 1.9
Education, y	8.9 \pm 1.8	8.9 \pm 2.1	8.3 \pm 1.8
Education of head of household, y	10.8 \pm 1.3	11.6 \pm 1.9	11.3 \pm 2.0
Mother's age at subject's birth, y	21.6 \pm 6.4	19.7 \pm 3.3	20.4 \pm 5.2
Months dating boyfriend	10.4 \pm 10.4	10.1 \pm 12.2	...
Postmenarchial age, y	3.9 \pm 3.2	4.9 \pm 4.0	5.1 \pm 4.6

*The differences between the three groups were not significant.

Table 2.—Sexual Activity and Previous Pregnancies Among the Three Groups of Black Female Adolescents

	Boyfriend Interviewed, N (%)	Boyfriend Refused Interview, N (%)	No Boyfriend, N (%)	P
Ever sexually active				
Yes	20 (64.5)	23 (60.5)	11 (25.0)	.0005
No	11 (35.5)	15 (39.5)	33 (75.0)	
Total	31	38	44	
Currently sexually active				
Yes	18 (58.1)	17 (44.7)	4 (9.1)	.0000
No	13 (41.9)	21 (55.3)	40 (90.9)	
Total	31	38	44	
Previous pregnancies				
0	25 (80.6)	29 (76.3)	41 (93.2)	...
1	6 (19.4)	9 (23.7)	2 (4.5)	
2	0 (0.0)	0 (0.0)	1 (2.3)	
Total	31	38	44	

Table 3.—Mean \pm SD of the Social Psychological, Attitudinal, and Knowledge Variables for Three Groups of Black Female Adolescents

	Boyfriend Interviewed (Mean \pm SD)	Boyfriend Refused Interview (Mean \pm SD)	No Boyfriend (Mean \pm SD)	P
Level of worry about becoming pregnant	3.4 \pm 1.5	3.2 \pm 1.5	2.9 \pm 1.5	...
Agree that having a baby would ruin life	3.8 \pm 1.3	3.2 \pm 1.3	3.9 \pm 1.0	.0118
Desired age at having next baby	21.8 \pm 6.2	23.1 \pm 5.8	22.6 \pm 3.6	...
Well-being	2.4 \pm 1.1	2.4 \pm 1.0	2.4 \pm 1.0	...
Health status	2.2 \pm 1.3	2.3 \pm 1.1	2.2 \pm 1.2	...
Feelings of failure	2.9 \pm 1.3	3.5 \pm 1.1	3.2 \pm 1.9	...
Self-esteem	15.4 \pm 3.7	16.3 \pm 3.7	14.2 \pm 4.0	.06
Locus of control	14.5 \pm 4.0	14.1 \pm 5.5	16.5 \pm 4.5	.05
Positive attitudes toward birth control	4.9 \pm 2.1	5.0 \pm 1.7	4.6 \pm 2.0	...
Correct knowledge about birth control	2.9 \pm 1.0	2.8 \pm 1.1	2.9 \pm 1.1	...
Positive attitudes toward health care	4.7 \pm 1.8	4.7 \pm 1.8	4.5 \pm 1.3	...
Anomia	2.4 \pm 1.3	2.3 \pm 1.7	2.8 \pm 1.4	...

nificantly higher ($P \leq .05$) external locus of control than females with a boyfriend (Table 3). Females whose boyfriends refused an interview had slightly higher self-esteem, but the differences were not statistically significant ($P = .06$). The three groups did not differ on any other social psychological variable.

Among subjects who had ever engaged in coitus, subjects whose boyfriends had been interviewed were using more effective contraceptive

methods than were reported by the other two groups, and stated that their current contraceptive use was related to planning to continue coitus (Table 4). Both groups of females with boyfriends reported higher boyfriend support of their use of birth control than sexually active subjects without one identifiable boyfriend. More of the subjects whose boyfriends refused an interview had been noncompliant with their birth control during the previous 12 months than

the other two groups.

Only 64.5% and 57.9% of the two groups of females with boyfriends had a current boyfriend at the 6-month follow-up (Table 5). However, significantly more of the girls whose boyfriend had been interviewed had the same boyfriend at the 6-month follow-up. Twenty-two percent of females without a boyfriend at the initial interview reported steady boyfriend 6 months later. When controlling for previous sexual activity significantly more of the sexually active subjects in all three groups had either the same or a new boyfriend at the 6-month follow-up than females who had initially reported never engaging in coitus (Table 6).

When controlling for previous sexual activity at the 6-month follow-up, the three groups did not differ significantly in the contraceptive methods used, contraceptive compliance, or the number of times they had engaged in unprotected coitus during the previous 6 months.

Among females whose boyfriend agreed to be interviewed ($n = 31$), considerable variation was found in their sexual and contraceptive behavior, knowledge, and attitudes. The males were significantly older and had completed more school grades than their girlfriends (Table 7). The females reported using birth control more often than was reported by their boyfriend and felt more pressure from their partners not to use birth control than was expressed by the males. The males reported first engaging in coitus at an earlier age, a greater coital frequency, larger number of sexual partners, and more pregnancy scares than their girlfriends (Table 7). The males also felt more positive about their girlfriends becoming pregnant and having a baby than was expressed by the females.

Although males and females differed in the mean scores of several attitudinal and behavioral variables, a number of the scales measured in the females were correlated with their boyfriend scores. The responses of the female and their boyfriends to the level of effectiveness of the birth control they used, coital frequency, number of sexual partners, and number of times pregnant or got a girl pregnant were moderately positively correlated with one another (Table 8). The males' and females' att

COMMENT

Table 4.—Birth Control Use at the Initial Interview by the Sexually Active Subjects in Each Group

	Boyfriend Interviewed, N (%)	Boyfriend Refused Interview N (%)	No Current Boyfriend N (%)	P
Current birth control				
Prescription	18 (90.0)	11 (47.8)	6 (54.5)	
Condom/spermicide	2 (10.0)	2 (8.7)	2 (18.2)	
None	0 (0.0)	10 (43.5)	3 (27.3)	.016
Current contraceptive use related to planning to continue coitus	18 (90.0)	11 (47.8)	7 (63.6)	.0134
Boyfriend supports birth control use	14 (70.0)	16 (69.6)	5 (45.5)	.0014
Previous noncompliance with birth control	5 (26.3)	10 (58.8)	1 (14.3)	.05

Table 5.—Boyfriend Status of the Black Girls in Each Group at the 6-Month Follow-up

	Boyfriend Interviewed, N (%)	Boyfriend Refused Interview, N (%)	No Boyfriend, N (%)	P
Boyfriend at 6 months				
Yes	20 (64.5)	22 (57.9)	10 (22.3)	
No	11 (35.5)	16 (42.1)	34 (77.7)	.0003
Total	31	38	44	
Same boyfriend	14 (54.5)	13 (34.2)	0 (0.0)	.0000

Table 6.—Boyfriend Status and Contraceptive Use at the 6-Month Follow-up by Sexually Active Subjects in Each Group

	Boyfriend Interviewed, N (%)	Boyfriend Refused Interview, N (%)	No Current Boyfriend, N (%)	P
Boyfriend status				
No boyfriend	6 (30.0)	6 (26.1)	6 (54.5)	...
New boyfriend	3 (15.0)	5 (21.7)	5 (46.5)	...
Same boyfriend	11 (55.0)	12 (52.2)	0 (0.0)	...
Total	20	23	11	
Pregnancies	2* (10.0)	3 (13.0)	0 (0.0)	...
Birth control				
Prescription	16 (80.0)	10 (43.5)	7 (63.6)	...
Condom/spermicide	0 (0.0)	3 (13.0)	2 (18.2)	...
Other	1 (5.0)	0 (0.0)	0 (0.0)	...
None	3 (15.0)	10 (43.5)	2 (18.2)	.095
Total	20	23	11	

*One additional pregnancy occurred in a subject who was not sexually active at the pretest.

tudes toward becoming pregnant and having a baby were also moderately correlated. However, the males' and females' responses to the frequency with which they engaged in coitus without using birth control was inversely correlated.

Among the social psychological variables, the females' self-esteem and anomia were inversely correlated with their boyfriends' scores. None of the other social psychological, attitudinal, or knowledge scales were significantly correlated.

We attempted to determine whether characteristics of the heterosexual relationship were associated with the sexual and contraceptive behavior of a sample of black female adolescents. Previous theoretical and empirical work suggest that the establishment of a long-term monogamous relationship will result in changes in both sexual and contraceptive attitudes and behaviors by adolescents.⁸⁻¹⁰ When an unmarried female adolescent first becomes sexually active, she usually does not accept her identity as a sexually active person. This incongruence between the adolescent's premarital sexual standards and her actual sexual behavior results in infrequent or sporadic sexual intercourse and a decreased chance that she will rationally consider the risk of pregnancy. The resolution of the incongruence between sexual values and behavior often occurs over time after the establishment of a monogamous heterosexual relationship. A stable monogamous relationship provides a rationale for coitus, creating a congruence between premarital sexual standards and behavior, and leading to an increase in acceptance of continuing coitus. With this change in sexual identity, the frequency of intercourse will increase, resulting in a heightened awareness of the possibility of pregnancy.⁸⁻¹⁰

Even if a female adolescent possesses a heightened perception of her risk of pregnancy following unprotected coitus, her use of birth control will partly depend on her partner's attitude toward contraception.^{8,10} Scales¹⁹ suggests that, because of a difference in sex roles, male adolescents tend to have more power in their sexual relationship than their female partners. This power differential can lead to pressure for the female to engage in coitus and adopt the male's lack of consideration for birth control.²⁰⁻²² In support of this proposition, Jorgensen et al²³ found that female adolescents who reported less decision-making power over sexual issues in their relationships engaged in a greater frequency of sexual intercourse than those who perceived themselves as having relatively more control.

Based on interviews with both the female and male adolescents in our study sample, we hypothesized that the

Table 7.—Paired t-Tests of Mean Differences Between Black Female Adolescents and Their Boyfriends for Sexual Behavior and Attitudes

	n	Girls Mean \pm SD	Boys Mean \pm SD	P
School grades	31	8.90 \pm 1.85	9.48 \pm 2.13	.01
Age	31	15.26 \pm 1.84	16.66 \pm 3.17	.001
Frequency of birth control used during coitus	19	3.53 \pm 0.77	2.63 \pm 1.06	.007
Pressure from partner not to use birth control	18	4.28 \pm 3.43	2.06 \pm 0.93	.015
Age at first coitus	20	14.00 \pm 1.65	12.25 \pm 2.65	.028
Coital frequency	31	1.61 \pm 1.58	2.48 \pm 1.09	.001
No. of current sexual partners	31	0.68 \pm 0.65	1.39 \pm 1.52	.005
No. of sexual partners in last 3 mo	31	0.74 \pm 0.68	1.71 \pm 1.63	.003
No. of pregnancy scares	29	0.48 \pm 0.78	1.17 \pm 1.31	.017
Negative attitude toward having a baby	21	3.38 \pm 1.24	2.38 \pm 1.12	.001
Positive attitude toward becoming pregnant	24	1.58 \pm 0.65	2.04 \pm 0.96	.018

Table 8.—Correlations Between Demographic Variables, Sexual Behavior, Attitude and Knowledge Variables, and Social Psychological Variables by Black Adolescent Girls and Their Boyfriends (n=31)

	r	P	τ	P
Age	.77	.0001	.61	.0001
School grade	.83	.0001	.76	.0001
Months dating	.42	.019	.35	.008
Level of effectiveness of birth control used	.60	.0001	.57	.001
Frequency of coitus in last month without using birth control	-.20	...	-.06	...
Coital frequency (presently)	.57	.001	.52	.001
Coital frequency in last month	.65	.002	.54	.003
No. of sexual partners (presently)	.53	.002	.54	.001
No. of times pregnant	.54	.002	.54	.003
Negative attitude toward having a baby	.54	.012	.44	.017
Positive attitude toward becoming pregnant now	.45	.028	.41	.035
Frequency of sexually transmitted diseases	.81	.0001	.59	.001
Self-esteem	-.40	.025	-.30	.026
Locus of control	.29	.11	.23	.08
Positive attitude toward birth control scale	.02	...	-.02	...
Knowledge of birth control scale	.0503	...
Positive attitudes toward physicians	-.16	...	-.11	...
Anomia	-.37	.066	-.23	...

females were involved in three distinctly different types of heterosexual relationships. Thirty-one subjects had boyfriends who agreed to undergo an extensive interview about their sexual

and contraceptive behavior and attitudes. These male and female adolescents reported to us that they communicated in a more open manner about their sexual relationships than was reported

by the other subjects, and the males exhibited a greater willingness to comply with their partners' request to be interviewed. In contrast, 38 females had one identifiable boyfriend each, all of whom refused their partner's requests to be interviewed. Although each of these females expressed a willingness for their boyfriends to participate in the study, they all reported a lack of open communication with their boyfriends about sexually related issues. In contrast with Jorgensen et al,² but in support of our previous hypotheses,⁸⁻¹⁰ fewer of the females in this group were currently sexually active than in the group of females whose boyfriends agreed to be interviewed. The third group of 44 subjects either did not have a boyfriend at the present time or could not identify one steady sexual partner. However, 22% of this group had steady boyfriends at the 6-month follow-up.

The females with boyfriends who agreed to be interviewed expressed more negative feelings about the possibility of having a baby, higher previous contraceptive compliance, used more effective contraceptive methods at the time of the interview, and were more likely to state that their use of birth control was due to their plans to continue their monogamous sexual relationship. These findings support the hypothesis that the character of the heterosexual relationship may be associated with the black female adolescents' sexual and contraceptive behaviors and attitudes. In contrast with Scales,¹⁹ these differences between the two groups of females with boyfriends were not due to their perception of their boyfriends' support of their use of contraception, the length of time they had been dating their boyfriends, the degree they felt in control of their own life or their attitudes and knowledge about birth control. The mechanism for these differences may lie with other factors associated with the stability of these subjects' heterosexual relationships.⁸⁻¹¹ At the 6-month follow-up, significantly more of the females whose boyfriends had been interviewed had the same boyfriends. Although we do not know why a greater proportion of these females maintained a stable relationship with their boyfriends, this group exhibited more responsible contraceptive behavior. Perhaps the longer the couple stays

together, the more likely they will be to communicate openly about sexually related issues. This increase in communication may result in the female adolescent feeling more comfortable with her decision to use contraception.⁸⁻¹⁰

A second objective of this study was to compare the 31 females' sexual and contraceptive behavior and attitudes with the behavior and attitudes of their boyfriends. In agreement with Freeman et al.,²⁰ the males reported more risk taking in their sexual and contraceptive behavior than their girlfriends. We also found that the females expressed feeling more pressure from their boyfriends not to use birth control than the males expressed they felt from their girlfriends, which supports the conclusions of both Scales¹⁹ and Jorgensen et al.²³ Males may also feel more positive about their girlfriends becoming pregnant and having a baby than was reported to be felt by the females. These gender differences in attitudes about having a baby are significant, considering that the self-esteem scale scores for males and females were moderately inversely correlated.

These data suggest that the risk of poor contraceptive behavior would be greatest among those couples where the male has a higher self-esteem and a positive attitude toward his girlfriend having a baby, and the female has a lower self-esteem and perceives a great deal of pressure from the male not to use birth control.

Although the mean scores of several of the attitudinal and behavioral variables differed significantly between the males and females, for many of these factors the males' and females' scores were moderately correlated. For example, although the males had less negative attitudes about the possibility of their girlfriends becoming pregnant and more positive attitudes toward their girlfriends having a baby, the couples' scores on these scales were moderately positively correlated. These findings suggest that the establishment of these relationships may have been partly based on these adolescents' similarity in attitudes and behavior.⁶ The longer the

relationship existed, the more opportunity the couples had to discuss their attitudes and beliefs about sex and birth control, and the more likely that congruence would occur in their sexual attitudes and behaviors.⁸⁻¹⁰ Billy et al.^{6,7} have reported that they were unable to find any similarity in sexual behavior between black adolescent males and females and their same-sex friends, and concluded that friendship choices were not based on sexual behavior. In comparison with Billy et al.,^{6,7} our findings of a moderate level of similarity in sexual attitudes and behavior suggest that black adolescent heterosexual relationship choices may be based partly on sexual attitudes and behaviors.

In conclusion, our data support the assumption that characteristics of the heterosexual relationship are associated with the sexual and contraceptive behavior of some black female adolescents. Although our sample was representative of the population from which it was drawn, the fact that the target group was from a black lower socioeconomic population from a southeastern city limits the national generalizability of the findings. However, this study reinforces the need for clinicians to inquire about the characteristics of an adolescent's sexual relationship during contraceptive counseling. Information such as the length of the relationship, number of sexual partners, frequency of sexual intercourse, the degree the couple communicates about their sexual relationship and contraceptive use, and the female's perception of her boyfriend's support of her use of birth control may be helpful indicators of the sexually active female's poor contraceptive behavior. Our findings also suggest that future research directed at adolescent sexuality, contraceptive behavior, and unwed pregnancy should continue to focus on the dynamics of interpersonal and sexual relationship development.

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WARNINGS: Under no circumstances should this vaccine be administered parenterally.

Administration of the vaccine should be postponed or avoided in those experiencing any acute illness and in those with any advanced debilitated condition or persistent vomiting or diarrhea.

Other viruses (including poliovirus and other enteroviruses) may interfere with the desired response to this vaccine, since their presence in the intestinal tract may interfere with the replication of the attenuated strains of poliovirus in the vaccine.

PRECAUTIONS: Preliminary data indicate that immune globulin (Human) (IG) does not appear to interfere with immunization with poliovirus vaccine live oral trivalent (OPV). However, until more data are available, it would seem prudent not to administer OPV shortly after IG, unless such a procedure is unavoidable, for example, with unexpected travel to or contact with epidemic areas or endemic areas. If OPV is given with or shortly after IG, the dose should probably be repeated after three months if immunization is still indicated.

The vaccine is not effective in modifying or preventing cases of existing and/or incubating poliomyelitis.

NATIONAL CHILDHOOD VACCINE INJURY ACT OF 1986 (as amended in 1987)

Manufacturer and lot number of vaccine administered must be recorded by health care provider in vaccine recipient's permanent record, along with date of administration and name, address, and title of person administering vaccine.

Health care provider must report to a health department or to the FDA the occurrence following immunization of any event set forth in the Vaccine Injury Table including: paralytic poliomyelitis—in a nonimmunodeficient recipient within 30 days of vaccination—in an immunodeficient recipient within 6 months of vaccination; any vaccine-associated community case of paralytic poliomyelitis; or any acute complication or sequela (including death) of above events.

Use in Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Poliovirus vaccine live oral trivalent. It is also not known whether OPV can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Although there is no convincing evidence documenting adverse effects of either OPV or IPV on the developing fetus or pregnant woman, it is prudent on theoretical grounds to avoid vaccinating pregnant women. However, if immediate protection against poliomyelitis is needed, OPV is recommended. (See **CONTRAINDICATIONS** and **ADVERSE REACTIONS**.)

ADVERSE REACTIONS: Paralytic disease following the ingestion of live poliovirus vaccines has been, on rare occasion, reported in individuals receiving the vaccine (see, for example, **CONTRAINDICATIONS**), and in persons who were in close contact with vaccinees. The vaccine viruses are shed in the vaccinee's stools for at least six to eight weeks as well as via the pharyngeal route. Most reports of paralytic disease following ingestion of the vaccine or contact with a recent vaccinee are based on epidemiological analysis and temporal association between vaccination or contact and the onset of symptoms. Most authorities believe that a causal relationship exists. Prior to administration of the vaccine, the attending physician should warn or specifically direct personnel acting under his authority to convey the warnings to the vaccinee, parent, guardian, or other responsible person of the possibility of vaccine-associated paralysis, particularly to susceptible family members and other close personal contacts.

The Centers for Disease Control report that during the years 1973 through 1984 approximately 274.1 million OPV doses were distributed in the US. During this same period, 105 vaccine-associated cases were reported (1 case per 2.6 million doses distributed). Of these 105 cases, 35 occurred in vaccine recipients (1 case per 7.8 million doses distributed), 50 occurred in household and nonhousehold contacts of vaccinees (1 case per 5.5 million doses distributed), 14 occurred in immunodeficient recipients or contacts, and 6 occurred in persons with no history of vaccine exposure, from whom vaccine-like viruses were isolated.

Thirty-three (94%) of the recipient cases, 41 (82%) of the contact cases, and 5 (36%) of the immune deficient cases were associated with the recipient's first dose of OPV. Because most cases of vaccine-associated paralysis have occurred in association with the first dose, the CDC has estimated the likelihood of paralysis in association with first v subsequent doses of OPV, using the number of births during 1973-1984 to estimate the number of first doses distributed, and subtracting this from the total distribution to estimate the number of subsequent doses distributed. This method estimates a frequency of paralysis for recipients of 1 case per 1.2 million first doses v 1 case per 116.5 million subsequent doses; for contacts one case per 1 million first doses v 25.9 million subsequent doses; with an overall frequency of 1 case per 520,000 first doses v 1 case per 12.3 million subsequent doses.

Other methods of estimating the likelihood of paralysis in association with OPV have been described. Because the number of susceptible vaccine recipients or contacts of recipients is not known, the true risk of vaccine-associated poliomyelitis is impossible to determine precisely.

When the attenuated vaccine strains are to be introduced into a household with adults who have not been adequately vaccinated or whose immune status cannot be determined, the risk of vaccine-associated paralysis can be reduced by giving these adults one dose of IPV per month for three months before the children receive Poliovirus vaccine live oral trivalent ORIMUNE. The children may receive the first dose of ORIMUNE at the same visit that the adult receives the third dose of IPV. The CDC reports that no paralytic reactions to IPV are known to have occurred since the 1955 cluster of poliomyelitis cases caused by vaccine that contained live polioviruses that had escaped inactivation.

The ACIP states: "Because of the overriding importance of ensuring prompt and complete immunization of the child and the extreme rarity of OPV-associated disease in contacts, the Committee recommends the administration of OPV to a child regardless of the poliovirus-vaccine status of adult household contacts. This is the usual practice in the United States. The responsible adult should be informed of the small risk involved. An acceptable alternative, if there is a strong assurance that ultimate, full immunization of the child will not be jeopardized or unduly delayed, is to immunize adults according to the schedule outlined above before giving OPV to the child."

The ACIP has concluded that "Oral polio vaccine remains the vaccine of choice for primary immunization of children."

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State-of-the-Art Reconstructive Surgery for Bladder Exstrophy at The Johns Hopkins Hospital

John P. Gearhart, MD, Robert D. Jeffs, MD

• **Bladder exstrophy is a congenital anomaly that has been difficult to correct. Advances in reconstructive surgery, some of which have originated at The Johns Hopkins Hospital, Baltimore, Md, have impacted on the care of these patients. We reviewed the progress made in patient care and the results of state-of-the-art treatment.**

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Reconstructive surgery for serious congenital anomalies has shown tremendous advances in the 100 years since Johns Hopkins endowed the hospital that bears his name. Bladder exstrophy is a devastating defect that illustrates this progress in treatment. The advance was given impetus by Hugh Hampton Young, the founder of the Brady Urological Institute, The Johns Hopkins Hospital, Baltimore, Md, and by other innovations from the same institution.

Early attempts at bladder closure to produce a urine receptacle failed due to dehiscence and infection or failed to produce continence. Trendelenburg,¹ in 1906, first attempted osteotomy as an adjunct to closure of the bladder, but the first sporadic success was reported by Burns² in 1924.

The lack of success in reconstruction led to many alternatives for urinary control, beginning with Magd³ in 1894 who successfully transplanted the trigone into the rectum. The ureterosigmoidostomy performed by Coffey⁴ and improved by Nesbit⁵ and Leadbetter and Clark⁶ became a popular alternative to closure, but ascending infection, hyperchloremic acidosis, and imperfect rectal continence prevented it from being a perfect solution. Adenocarcinoma

at the ureterocolic anastomosis has also dampened enthusiasm for its use. The Boyce-Vest procedure,⁷ Heitz-Boyer-Hovalacque procedure,⁸ ileal conduit,⁹ colon conduit,¹⁰ and colocolostomy with internal diversion have all been used to treat incontinence when bladder closure was impossible or failed.

External and internal diversion may still be required for classical exstrophy when the bladder is represented by a fibrous patch and other complicating anomalies prevent closure or subsequent growth of the bladder. The ideal reconstruction is directed to accomplish closure of the abdominal wall and bladder with subsequent correction of reflux, bladder neck revision for continence, and anatomical and functional repair of the epispadias.

Young¹¹ described the first female patient with urinary continence following repair for exstrophy in 1942 at The Johns Hopkins Hospital. Failure to correct reflux, recurrent infection, and intermittent incontinence marred what had seemed at first a great success. Dees,¹² in 1949, described a method of reconstructing the bladder neck in the related condition of complete epispadias with incontinence. These early contributions might be said to have stimulated others in the field of surgery to renew efforts toward successful reconstruction in this condition.

Contributions to the management of exstrophy reads like a list of prominent urologists, pediatric urologists, and pediatric surgeons who have practiced during the last 35 years. The names of Williams and Keaton,¹³ Shultz,¹⁴ Cendron,¹⁵ Marshall and Muecke,¹⁶ Lattimer et al,¹⁷ Culp,¹⁸ Ansell,¹⁹ Johnston and Kogan,²⁰ and Chisholm²¹ are among early contributors to reconstruction and the understanding of exstrophy.

The Johns Hopkins Hospital has had special interest in the exstrophy prob-

lem during the past 15 years, with publications addressing many facets of this problem. These include factors in successful closure,²² cause of wound dehiscence,²³ muscarinic cholinergic receptors,²⁴ inheritance of classical exstrophy,²⁵ incidence of malignancy,²⁶ urodynamic assessment during bladder neck plasty,²⁷ augmentations in failed closure,²⁸ and the effect of preliminary epispadias repair on bladder volume.²⁹

Contributions from many centers have addressed epispadias repair,^{30,31} urodynamics in exstrophy,³² factors in success,³³ staged closure using colon,³⁴ and the use of artificial sphincter in exstrophy.³⁵

The great interest, the diversity of opinion, and the variety of techniques attest to the difficulty of reaching an ideal solution in every patient. In general, the advances that have led to improved success include (1) early closure with better preservation of bladder epithelium and underlying muscle, (2) technical improvement in initial closure including penile lengthening and osteotomy when necessary, (3) management of reflux after initial closure and at the time of bladder neck reconstruction, (4) staged repair allowing for bladder growth and increased volume before bladder neck plasty for incontinence, (5) Leadbetter³⁶ trigonal tubularization after ureteral relocation, (6) preliminary epispadias repair to encourage bladder adaptation at low pressure to increase volume,²⁹ and (7) adjuncts to the surgical plan and technique.³⁷

This latter category cannot be minimized when one considers that antibiotics permit the contaminated bladder to be closed as a sterile wound. Monofilament and polyglycolic acid sutures have reduced reaction in wounds and helped to prevent foci of infection and wound reaction to gut sutures. Anticholinergics, sedatives, analgesics, and im-

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proved drainage techniques have kept the bladder and ureter at rest while healing occurred. Immobilization by traction or external fixation is important to maintain approximation of the anterior pelvic and fascial closure.

STAGED APPROACH

Not all patients present at birth with large bladders and an adequate phallus. The Table presents the options suggested by various ages and stages of presentation. Provision is made in the table both for the good bladder leading to successful closure and for the small bladder or others that fail to allow completion of the ideal plan.

THE ANOMALY

"In classical exstrophy no structure would seem missing," said Muecke in 1964. The defect in this anomaly (Figure) can be considered a midline separation with foreshortening of the distance between umbilicus and anal opening, with varying degrees of underdevelopment of bladder, urethra, and phallus. Classical exstrophy is the most common condition in a spectrum, ranging from penile epispadias to cloacal exstrophy. Classical exstrophy occurs in approximately 1 in 30 000 births. Shapiro et al²⁵ estimated the risk of recurrence in siblings as 1 in 300 and in offspring of patients with exstrophy as 1 in 70. Associated problems frequently seen in exstrophy are diastasis of the pubis, vesicoureteral reflux after closure, inguinal hernia, anterior displacement of the anus and sphincter mechanism, and short urethral groove. Gonadal and ductal abnormalities in both male and female patients do not appear to be part of the complex.

OSTEOTOMY

The newborn pelvis can be molded to allow midline closure of pubis and rectus fascia. This closure is sometimes difficult to hold, as the defect may be so wide that closure is difficult. Consideration should be given to each case to determine the need for osteotomy. Shultz²⁴ described the posterior iliac osteotomy, but more recently Sponseller et al³⁸ demonstrated the effectiveness of anterior transverse innominate osteotomy in promoting apposition of either initial closure or reclosure after partial or incomplete dehiscence. Firm anterior closure of the intersymphyseal bar

Management Plan for Bladder Exstrophy		
Age	Problem	Possible Solution
Initial Presentation of Patients With Bladder Exstrophy		
0-72 h	Classic exstrophy with capacity and moderate symphyseal separation; long urethral groove; mild dorsal chordee	I. Midline closure of bladder, fascia, and symphysis to level of posterior urethra; no osteotomy
0-72 h	The above findings with short urethra and severe chordee	II. Close as above, adding lengthening of dorsal urethral groove by paraexstrophy skin
0-72 h or late presentation	The above with very wide separation of symphysis or late presentation of patient (beyond 72 h to 1-3 y) for initial treatment	Iliac osteotomy and closure as in I or II
0-2 wk	Male penis duplex or extremely short	Consider female sex of rearing and closure as in I or II
0-2 wk	Very small nondistensible bladder patch	Prove by examination under anesthesia then nonsurgical expectant treatment awaiting internal or external diversion; experimental early augmentation by bowel and other material has been tried
The Incontinent Period After Initial Closure		
1 mo to 3 y	Infection with residual due to outlet stenosis	Urethral dilatation; occasional meatotomy or bladder neck revision
	Infection, grade III reflux with pliable outlet resistance	Continuous antibiotic suppression with plan for early ureteroneocystostomy
	Partial dehiscence at bladder neck or partial prolapse of bladder (both prevent bladder capacity increase)	Reclosure of bladder neck with or without osteotomy
Continence and Epispadias Repair		
2½-5 y	Closed bladder with incontinence; normal intravenous pyelogram; bladder capacity of 60 mL or more under general anesthesia; bilateral reflux; good penile size and length of urethral groove	Plan bilateral ureteroneocystostomy, bladder neck reconstruction, epispadias repair followed by 3 wk suprapubic drainage; prepare 5 wk and 2 wk before surgery with two 2-mg/kg injections of testosterone in oil
2½-5 y	As above with small bladder capacity (<60 mL)	Epispadias repair only after preparation with testosterone; bladder capacity will improve postoperatively

Continued on p 1477.

provides support and stability for the subsequent bladder neck plasty and may improve the efficacy of puborectalis and levator ani muscles.

RECONSTRUCTION OF THE BLADDER NECK

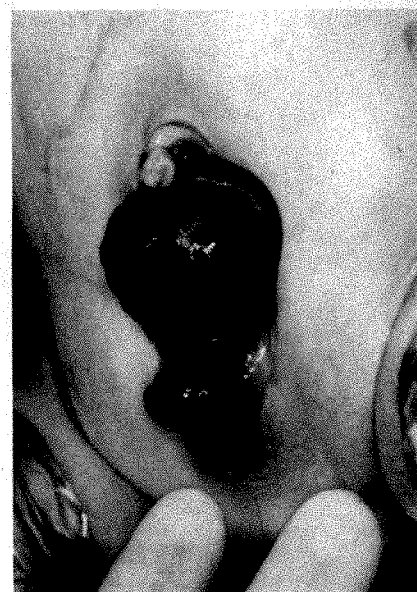
The initial stage of exstrophy management involves closure of bladder without attempts to produce continence. In the subsequent interval, free drainage aids in preventing upper tract infection and minimizes the problems from reflux. The uninfected bladder can then adapt at low pressure to urine that may accumulate at rest. The adaptation process may be encouraged by preliminary epispadias repair at 2 years of age. A capacity of 60 mL as judged under general anesthesia is desirable before proceeding with bladder neck plasty. The procedure³⁹ is a modification of the Leadbetter procedure using the Cohen⁴⁰ antireflux operation to reimplant and

relocate the ureters, followed by tubularization of the trigone and suspension of the bladder neck. Urinary diversion and minimization of bladder spasms is required to allow firm healing of the repair. Voiding trials are begun after 3 weeks of diversion. Voluntary detrusor contractions may not exist at first, gentle dilation by catheter may be required, and weeks or months may be needed to develop a useful dry interval and nocturnal control.

RESULTS

First-stage closure of the exstrophied bladder is not always successful as seen in the review of 20 patients treated for wound dehiscence after primary closure.²³ Although reclosure is possible, subsequent result of reconstruction may be disappointing. Primary closure was selected in 28 of 29 consecutive patients referred to The Johns Hopkins

Management Plan for Bladder Exstrophy (cont)		
Age	Problem	Possible Solution
	Epispadias repaired; bladder capacity greater than 60 mL	Proceed to bladder neck plasty and ureteroneocystostomy
	Epispadiac penis short with severe chordee before or after bladder neck reconstruction	Correction of chordee, lengthening of urethral groove, and epispadias repair; prepare with testosterone; consider osteotomy to aid in achieving penile length
3+ y	Complete repair of bladder, bladder neck, and epispadias with dry interval but wet pants	Patience, biofeedback, oxybutynin hydrochloride (Ditropan), imipramine hydrochloride, and time
	Above, with marked stress incontinence	Wait; may require bladder neck revision or injection
	Small-capacity bladder unchanged by time, epispadias repair, or attempted bladder neck reconstruction	Consider augmentation cystoplasty and bladder neck reconstruction; acceptance of intermittent catheterization will be necessary
3-7 y	Small bladder unsuitable for bladder neck plasty	Consider temporary diversion by colon conduit with plan for continent undiversion to bladder using bladder to form urethra and conduit for augmentation; in patients over 7 y, artificial sphincter can be considered
3-7 y	Small closed exstrophy unsuitable for bladder neck reconstruction or augmentation, or late presentation of untreated exstrophy, unsuitable for closure	Consider permanent external or internal diversion or continent urinary diversion, internal diversion direct by ureterosigmoidostomy or indirect colocolostomy; evaluate day continence of anal sphincter and nighttime seepage prior to internal diversion
5-15 y	Closed exstrophy with epispadias repaired with uncontrolled stress or dribbling incontinence	Consider revision, injection, augmentation and revision, continent urinary diversion, and artificial sphincter with omental wrap
10-20 y	Closed or diverted exstrophy with inadequate penis	Consider penile lengthening, urethral reconstruction with augmentation using free graft, pedicle grafts, and tissue transfer



Male neonate with bladder exstrophy. The umbilicus, exstrophied bladder, and complete epispadias associated with this condition are shown.

Hospital without prior treatment. One patient underwent urinary diversion because of a very small bladder. Mild bladder prolapse occurred in 2 patients who required distal revision of the closure. The remainder had satisfactory initial closure.⁴¹

Marshall and Muecke¹⁶ in 1970 reviewed 329 functional bladder closures reported in the literature between 1906 and 1966 and determined that urinary continence with preservation of renal function was achieved in only 16 (5%) of the cases.

When staged reconstruction is used similar to what is described above, better continence results are obtained as reported by Chisholm²¹ (45% continent), Ansell¹⁹ (43% continent), and Mollard⁴² (69% continent).

Oesterling and Jeffs,⁴³ in review of the The Johns Hopkins Hospital experience of 144 patients seen between 1975 and 1985, selected 50 patients who had completed staged reconstruction. Two

groups of patients were compared: group A (39 patients) had had successful initial closure while group B (11 patients) had required reclosure of the bladder after partial or complete dehiscence. Group A patients had a continence rate of 92%, while in group B only 55% became continent.

In follow-up, 88% of these groups had normal upper tracts, while 6% had persistent reflux requiring additional treatment, and 6% (3 patients) required additional treatment for hydronephrosis.

When continence is not achieved in patients with adequate bladder capacity, additional repeated bladder neck plasty may be performed or injection of polytetrafluoroethylene (Teflon) or collagen can be considered.

THE FAILED RECONSTRUCTION

When continence is not achieved, when the bladder remains too small to

proceed with bladder neck revision, or when hydronephrosis develops, techniques of salvage are well established. Twelve such patients treated at The Johns Hopkins Hospital are described by Gearhart and Jeffs.²⁸ All had augmentation cystoplasty and used intermittent catheterization; in addition, repeated bladder neck plasty in four patients, artificial sphincter in three, and Mitrofanoff procedure in one were required. Artificial sphincter is usually reserved for the older patient where omentum can be used to protect the urethra from the sphincter cuff.

LONG-TERM FOLLOW-UP

Newer techniques for correction of chordee and repair of epispadias can achieve reasonable penile length and erection. Details of epispadias repair will not be discussed in this presentation. However, all patients followed up in our local experience have erections and older patients have a normal libido. Penile length and chordee corrector are problems in some patients. Fertility in the male patient has been documented by sperm count⁴⁴ and in the report of Shapiro et al,²⁵ 38 men had fathered children. Possible injury to the ejaculatory ducts and retrograde ejaculation are a concern in the individual patient who has undergone reconstruction.

One hundred thirty-one women have delivered children²⁵ and most of these would have undergone early diversion of the urine. Reconstruction for continence should dictate delivery by cesarean section when pregnancy occurs, due to possible danger of damage to the bladder neck.

Adenocarcinoma⁴⁶ in untreated exstrophy is well known in older patients. Engel and Wilkinson²⁶ have reviewed malignancy of the bladder in exstrophy, and to date there are three patients who have developed rhabdomyosarcoma in the exstrophied bladder and two patients who underwent late closure have developed squamous cell carcinoma, while no patient who has undergone early closure has developed epithelial tumor.⁴⁶ However, long-term surveillance is mandatory in these patients.

When urinary diversion is chosen, malignancy of the bowel wall is a concern; in ureterosigmoidostomy, 10% of patients after 10 years may develop adenocarcinoma.⁴⁷

Social adjustment in a series of older patients with exstrophy reviewed by Lattimer et al¹⁷ was considered good in 13 of 17 patients. Woodhouse et al⁴⁸ found 55 of 64 patients gainfully employed and well adjusted. The recent series from The Johns Hopkins Hospital indicates that patients who underwent reconstructed exstrophy appear to have normal interactions at home and at school. Of course, long-term follow-up is required.

CONCLUSION

Early successful closure, careful management of the incontinent period, and a good technical bladder neck plasty can result in a patient with normal control and normal upper tracts. The small bladder removed from external irritation will increase in size and can be helped by preliminary epispadias repair if needed. Bladder neck reconstruction should not be attempted until the bladder reaches a capacity of 60 mL. Epispadias repair has many variations and these have not been detailed here. Lengthening of the urethral groove is often required and stimulation with testosterone is helpful in preparation for penile surgery.⁴⁹

Augmentation,²⁸ intermittent catheterization, Mitrofanoff procedure,⁵⁰ and continent diversion⁵¹ are salvage techniques that provide capacity for the

small or unusual bladder and for those whose reconstruction is unsuccessful.

This report was submitted in honor of The Johns Hopkins Hospital 1889 to 1989 centennial.

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Radiological Cases of the Month

Barbara E. Magera, MD, PharmD; Sarah G. Klein, MD;
C. Warren Derrick, Jr, MD (*Contributors*); Beverly P. Wood, MD (*Section Editor*)



Figure 1.



Figure 2.

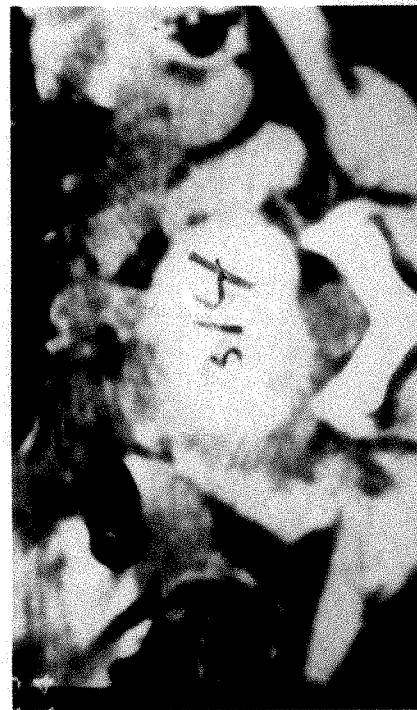


Figure 3.

A 2½-year-old white boy was seen by his pediatrician because of increasing irritability and unsteady gait. Three months prior to admission the youngster had fallen down a flight of stairs without apparent injury. Several days prior to admission, the child experienced progressive low back pain and stiffness.

The boy's medical history was remarkable for multiple episodes of oti-

tis media and upper respiratory tract infections requiring medical therapy. The patient completed a 10-day course of antibiotic therapy as recently as 1 month prior to injury.

On admission, the patient was afebrile and the results of the physical examination were normal except for a wide-base gait and pronounced lumbar lordosis. Admission laboratory values were as follows: white blood cell count, $13 \times 10^9/L$, with 0.70 polymorphonuclear leukocytes; hemoglobin level, 116 g/L; hematocrit value, 0.33; platelet count, $504 \times 10^9/L$; erythrocyte sedimentation rate (Westergren), 13 mm/h; and the complement profile was C3, 1.48 g/L, and C4, 0.28 g/L. The C-reactive protein was positive. The result of a tuberculin skin test

was negative. The results of the urinalysis were normal. Blood and urine cultures were negative.

A technetium pyrophosphate bone scan (Fig 1) and roentgenograms of the lumbosacral spine (Fig 2) were obtained. Unenhanced computed tomography was also performed (Fig 3).

Based on the roentgenographic and computed tomographic findings showing narrow disk space, and the negative cultures, a presumptive diagnosis of diskitis rather than vertebral osteomyelitis was made. Magnetic resonance imaging of the affected area showed loss of the normal disk signal intensity on T_1 images and increased signal intensity within the involved vertebral bodies on T_2 images (Fig 4). Thickening of adjacent paravertebral

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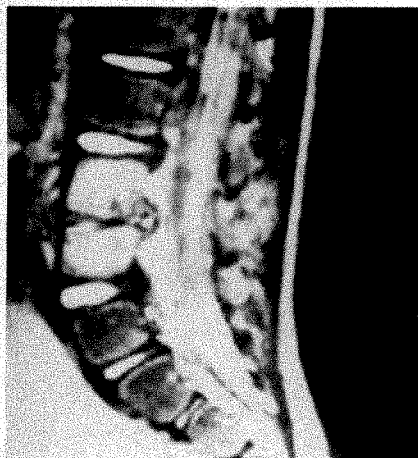


Figure 4.

soft tissue was noted. Needle aspiration of the L3-4 disk space yielded normal findings. The patient was treated with ceftriaxone (50 mg/kg per day) and nafcillin (100 g/kg per day) for 2 weeks, followed by 4 weeks of oral cephalexin (100 mg/kg per day), with marked clinical improvement. One month after presentation, the patient was asymptomatic.

Diskitis is a self-limited inflammation of the intervertebral disk space that occurs primarily in children.¹⁻⁶ The peak incidence occurs at 2 to 3 years of age^{2,5,7} with girls outnumbering boys by 2 to 1.⁷ The majority of cases involve the lumbar spine.^{1,3,4,6,8,9} Although not a requirement for diagnosis,^{3,8} pathogens isolated from aspiration biopsy include *Staphylococcus aureus*^{1,3,4} or, occasionally, *Haemophilus influenzae*.⁷

In contrast to vertebral osteomyelitis, children with diskitis generally are not systemically ill.² Fever may not be present, and the total and differential white blood cell counts may be normal. Often, the only laboratory abnormality may be an elevated erythrocyte sedimentation rate.^{1-6,8}

Diskitis is a clinical diagnosis that, because of its variable presentation, requires a high index of suspicion.^{3,5,6,8} Children with diskitis frequently present with vague, low back pain and difficulty or refusal to sit up, walk, or bear weight.¹⁻¹¹ Generally, the child refuses to assume any position that flexes the spine.^{3,5,7,8} The physical examination reveals abnormal posturing with exaggerated lumbar lordosis^{2,6} or

Fig 1.—Technetium pyrophosphate bone scan showing increased uptake of isotope at L3-4.

Fig 2.—Lateral roentgenogram of the lumbosacral spine revealing narrowing of the L3-4 disk space with irregularity of the adjacent end plates.

Fig 3.—Unenhanced computed tomographic scan showing narrowing of the disk space and cortical irregularity of adjacent vertebral bodies.

Fig 4.—Magnetic resonance image of the affected area showing loss of the normal disk signal intensity of T₁ images.

a change in gait pattern without neurological findings.^{4,7} Percussion and/or palpation of the lumbar spine does not reliably reproduce symptoms.

Although the exact etiology of diskitis is unclear,⁸ preceding trauma may be the inciting event.^{2,5} In children, the vascular supply of the disk space branches from adjacent vessels supplying the vertebral bodies.^{2,3,5,10} Trauma with a resulting separation of the vertebral end plates and disruption of the vascular supply, in the presence of transient bacteremia, may allow the entrance of pathogens into the vertebral disk space.^{2,3,5,8} In contrast, by the third decade, the disk space is largely avascular,^{2,3} and infectious inflammation of the disk is likely the result of progressive vertebral osteomyelitis.^{1,5}

Despite various treatment modalities, ranging from total body cast immobilization to strict bedrest with or without antibiotic treatment, children have recovered without sequelae.^{1,5,8} Surgical decompression with open diagnostic biopsy is not routinely advocated.^{3,5,8} Early diagnosis is important to accurately rule out more serious and potentially treatable conditions, such as osteomyelitis, septic arthritis, tuberculosis (Pott's disease), meningitis, or spinal tumors.

The classical findings of disk space narrowing and loss of the superior vertebral notch observed on lateral spine roentgenograms may not be evident until 2 to 8 weeks after the onset of symptoms.¹⁻⁷

Technetium or gallium bone scans may provide roentgenographic evidence as early as 1 week after symptoms appear.^{5,7,12} However, the use of gallium in infants is discouraged due

to the greater radiation exposure.⁶ Additionally, normal results of gallium or technetium bone scans do not exclude diskitis.⁸

We describe a case of a patient with diskitis that was confirmed by magnetic resonance imaging. Magnetic resonance imaging distinguishes disk inflammation from pyogenic bone lesions and is rapid, accurate, and non-invasive. The role of magnetic resonance imaging will require more widespread use and clinical evaluation before becoming the radiologic procedure of choice for the diagnosis of diskitis in children.

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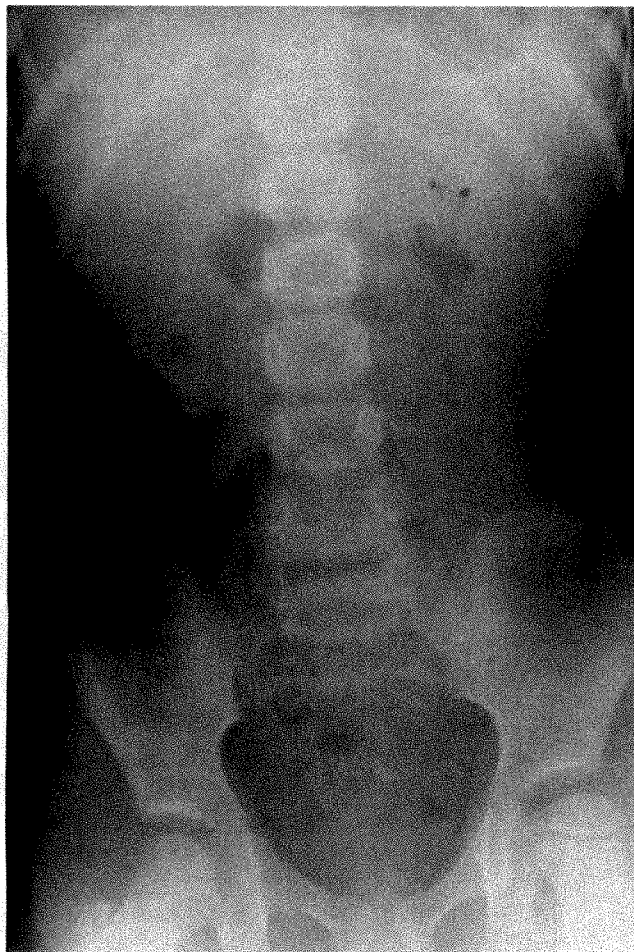


Figure 1.

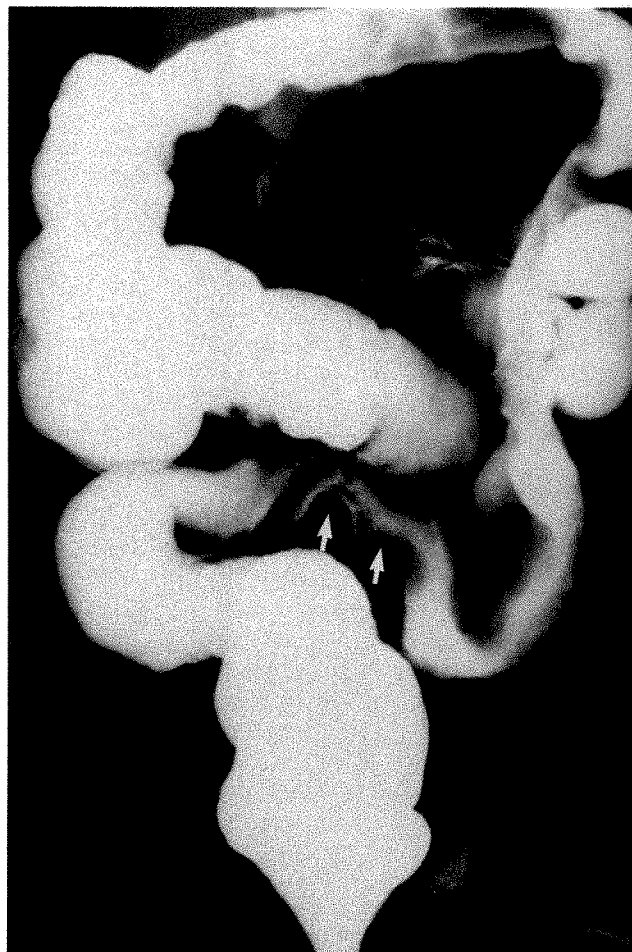


Figure 2.

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A 4-year-old, previously well girl was admitted to an outside hospital with an acute illness consisting of abdominal pain, watery diarrhea, and nonbilious vomiting. She was presumed to have an acute gastroenteritis with dehydration. She was transferred to our institution 48 hours later after her diarrhea became bloody. The

patient's white blood cell count was $39 \times 10^9/L$ and rising, her platelet count was $90 \times 10^9/L$ and falling, and her hemoglobin level was 100 g/L and falling. Only erythematous mucosa was found at proctoscopy. Abdominal roentgenography (Fig 1) and barium enema examination (Fig 2) were performed.

Denouement and Discussion

Gastrointestinal Manifestations of Hemolytic Uremic Syndrome

Fig 1.—Plain roentgenogram of the abdomen showing no evidence of toxic megacolon, fixed loops of bowel, or intussusception.

Fig 2.—Barium enema examination shows thickened folds (arrows) representing edema and hemorrhage in the submucosa mucosal spiculation representing inflammation, and patulous terminal ileum representing ileitis.

Hemolytic uremic syndrome (HUS) is a disease of unknown origin usually occurring in children younger than 4 years. The pathologic findings resemble a microangiopathy and are associated with an angiitis and the formation of platelet thrombi resulting in the classic triad of hemolytic anemia, thrombocytopenia, and azotemia. Hemolytic uremic syndrome may belong with a continuum of disease, including thrombotic thrombocytopenia purpura. Characteristically, there is a prodromal illness that is most commonly a nonspecific gastroenteritis. This is followed in 1 to 2 weeks by the development of a variable number of presenting abnormalities, including pallor, purpura, abdominal pain, hematuria, oliguria, hematemesis, and bloody diarrhea. Therefore, HUS may be mimicked by a number of entities, including glomerulonephritis, He-

noch-Schönlein purpura, nephrotic syndrome, and myelophthisic diseases. As with our patient, HUS may occasionally mimic inflammatory bowel disease.^{1,2} More rarely, gastrointestinal presentations include toxic megacolon or rectal prolapse.³ The bowel wall thickening and "thumb printing" seen in our patient was most likely due to submucosal hemorrhage (Fig 2). During its course, HUS has diffuse manifestations reflecting widespread microangiopathy. Prominent signs of this multisystem involvement include hypertension, fluid and electrolyte imbalance, bleeding diatheses, seizures, coma, nephrotic syndrome, colitis, myocarditis, and hepatomegaly.

Our patient's normal renal function deteriorated rapidly, requiring hemodialysis management. Complete recovery occurs in 1 to 3 weeks in most

children who are medically supported, but complications can prolong this recovery period. Anuria can be successfully treated with dialysis, but some children suffer from chronic renal insufficiency. The mortality rate in the 1970s was between 10% to 20% but has decreased considerably with the more widespread use of early dialysis. Poor prognosis is related not only to the severity of the renal involvement, but also more importantly to the severity of extrarenal, especially central nervous system, involvement.

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The Editors welcome contributions to PICTURE OF THE MONTH and RADIOLOGICAL CASE OF THE MONTH. Those who wish to contribute should send their manuscripts to Dr Feingold (Picture of the Month), National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135, or Dr Wood (Radiological Case of the Month), University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.



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Please see adjacent page for brief summary of prescribing information.
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NIX[®] FOR LICE[®]

CREME RINSE

permethrin 1%

*Nix
Disp 2 fl oz
Sig. as
directed on bottle
label
Tom Smith, MD*

PEDICULICIDAL/OVICIDAL ACTIVITIES: *In vitro* data indicate that permethrin has pediculicidal and ovicidal activity against *Pediculus humanus* var. *capitis*. The high cure rate (97-99%) of Nix in patients with head lice demonstrated at 14 days following a single application is attributable to a combination of its pediculicidal and ovicidal activities and its residual persistence on the hair which may also prevent reinfestation.

INDICATIONS AND USAGE: Nix is indicated for the single-application treatment of infestation with *Pediculus humanus* var. *capitis* (the head louse) and its nits (eggs). Retreatment for recurrences is required in less than 1% of patients since the ovicidal activity may be supplemented by residual persistence in the hair. If live lice are observed after at least seven days following the initial application, a second application can be given.

CONTRAINDICATIONS: Nix is contraindicated in patients with known hypersensitivity to any of its components, to any synthetic pyrethroid or pyrethrin, or to chrysanthemums.

WARNING: If hypersensitivity to Nix occurs, discontinue use.

PRECAUTIONS:

General: Head lice infestation is often accompanied by pruritus, erythema, and edema. Treatment with Nix may temporarily exacerbate these conditions.

Information for Patients: Patients with head lice should be advised that itching, redness, or swelling of the scalp may occur after application of Nix. If irritation persists, they should consult their physician. Nix is not irritating to the eyes; however, patients should be advised to avoid contact with eyes during application and to flush with water immediately if Nix gets in the eyes. In order to prevent accidental ingestion by children, the remaining contents of Nix should be discarded after use.

Combing of nits following treatment with Nix is not necessary for effective treatment. However, patients may do so for cosmetic or other reasons. The nits are easily combed from the hair treated with Nix after drying.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Six carcinogenicity bioassays were evaluated with permethrin, three each in rats and mice. No tumorigenicity was seen in the rat studies. However, species-specific increases in pulmonary adenomas, a common benign tumor of mice of high spontaneous background incidence, were seen in the three mouse studies. In one of these studies there was an increased incidence of pulmonary alveolar-cell carcinomas and benign liver adenomas only in female mice when permethrin was given in their food at a concentration of 5000 ppm. Mutagenicity assays, which give useful correlative data for interpreting results from carcinogenicity bioassays in rodents, were negative. Permethrin showed no evidence of mutagenic potential in a battery of *in vitro* and *in vivo* genetic toxicity studies. Permethrin did not have any adverse effect on reproductive function at a dose of 180 mg/kg/day orally in a three-generation rat study.

Pregnancy: Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits (200-400 mg/kg/day orally) and have revealed no evidence of impaired fertility or harm to the fetus due to permethrin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the evidence for tumorigenic potential of permethrin in animal studies, consideration should be given to discontinuing nursing temporarily or withholding the drug while the mother is nursing.

Pediatric Use: Nix is safe and effective in children two years of age and older. Safety and effectiveness in children less than two years of age have not been established.

ADVERSE REACTIONS: The most frequent adverse reaction to Nix is pruritus. This is usually a consequence of head lice infestation itself, but may be temporarily aggravated following treatment with Nix. 5.9% of patients in clinical studies experienced mild temporary itching; 3.4% experienced mild transient burning/stinging, tingling, numbness, or scalp discomfort; and 2.1% experienced mild transient erythema, edema, or rash of the scalp.

DOSE AND ADMINISTRATION:

Adults and Children: Nix is intended for use after the hair has been washed with shampoo, rinsed with water and towel dried. Apply a sufficient volume of Nix to saturate the hair and scalp (especially behind the ears and on nape of the neck). Nix should remain on the hair for 10 minutes before being rinsed off with water. A single treatment is sufficient to eliminate head lice infestation. Combing of nits is not required for therapeutic efficacy, but may be done for cosmetic reasons or to meet school "no nit" policies. A nit comb is provided.

SHAKE WELL BEFORE USING.

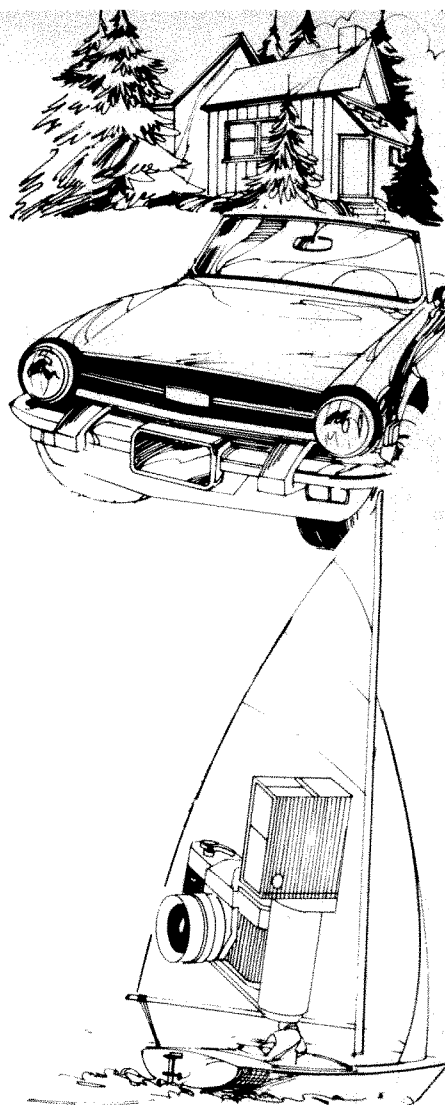
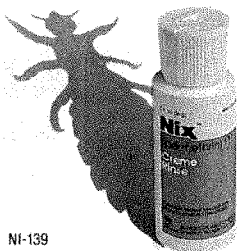
HOW SUPPLIED: Nix (Permethrin) 1% (wt./wt.) Creme Rinse is supplied in plastic squeeze bottles that contain 2 fl. oz. weighing 56 g. (NDC-0081-0780-81)
Store at 15°-25°C (59°-77°F).

References:

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Partition of Nitrogen Intake and Excretion in Low-Birth-Weight Infants

Sharon M. Donovan, PhD, RD; Stephanie A. Atkinson, PhD; Robin K. Whyte, MB, FRCPC; Bo Lönnerdal, PhD

• Although nitrogen balance studies have been carried out in low-birth-weight infants, few have partitioned the nitrogen into its components. In this study, 72-hour balance studies were conducted in 24 low-birth-weight infants (gestational age, 30.7 ± 1.6 weeks; birth weight 1.36 ± 0.25 kg) fed their mothers' milk (preterm milk) or 50% preterm milk and 50% formula. Total nitrogen, nonprotein nitrogen, and whey protein intake and excretion were measured. Total nitrogen intake (preterm milk group, 452 ± 138 mg/kg per day; preterm + formula group, 406 ± 93 mg/kg per day), absorption (85%), and retention (71%) were not significantly different between groups. Intact and fragments of secretory IgA and lactoferrin were detected in soluble fecal extracts, and represented 25% and 9% of intake, respectively. Feeding preterm milk allows for nitrogen accretion similar to intrauterine growth rates for 5 weeks postnatally, and provides potentially functional proteins for the low-birth-weight infant.

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The early neonatal period is characterized by high nutrient requirements and immature digestive and excretory capacities. Human milk meets the nutritional needs of term infants without exceeding their physiological limitations¹; however, the premature infant has higher nutrient requirements than the term infant, coupled with less well-developed gastrointestinal functions. Therefore, the suitability of mature human milk, particularly banked human milk, as a source of energy, protein, and minerals for the premature infant has been questioned.^{2,3} Atkinson et al⁴ reported that the nitrogen content of milk from mothers delivering prematurely ("preterm milk" [PTM]) was significantly higher than the nitrogen con-

centration of term milk for the first month of lactation. Preterm milk contains higher concentrations of protein, macrominerals, energy, and electrolytes,^{4,8} which led to the speculation that the optimum food for the premature infant may be the milk of the infant's mother.^{9,10}

Nitrogen in human milk is present as protein nitrogen and nonprotein nitrogen (NPN). Protein nitrogen is derived from both casein and whey proteins and constitutes approximately 75% of the nitrogen in mature human milk.¹¹ Several whey proteins may have important functions in the suckling infant,^{12,13} including secretory IgA (sIgA), lactoferrin, lipase, and lysozyme. Each of these proteins is believed to act within the gut via different bacteriostatic or immunologic mechanisms to protect the infant, including preventing attachment of bacteria and viruses to cells within the intestine,¹⁴ sequestering of nutrients,¹⁵ or causing lysis of bacteria.¹⁶ For these proteins to be functional, they must remain intact throughout at least part of the infant's gastrointestinal tract.¹² Identification of immunologically intact sIgA, lactoferrin, and lysozyme in the feces of human milk-fed term^{15,17,18} and premature^{19,20} infants provides support for this hypothesis.

Nonprotein nitrogen is composed of a diverse group of low-molecular-weight compounds and accounts for 25% of the total nitrogen.^{11,21} The function of NPN in the nutrition of human milk-fed infants is still unclear, although nutritional and functional roles have been proposed. Urea nitrogen and free amino acids may provide nitrogen essential for synthesis of nonessential amino acids,²² whereas peptide hormones²³ and growth factors²⁴ may serve physiological rather than nutritional functions for the infant.

The goals of this study were, first, to investigate the adequacy of feeding solely PTM, compared with a combination of PTM and infant formula, on overall nitrogen retention; and second, to

quantitate and partition total nitrogen intake and excretion, as protein nitrogen (including the whey proteins) and NPN components.

PATIENTS AND METHODS

Subjects

Low-birth-weight infants ($n = 24$; 12 male, 12 female) were selected from the neonatal unit of Chedoke-McMaster Hospitals, McMaster Health Sciences Centre, Hamilton, Ontario. Infants were included in the study based on the following criteria: birth weight less than 1.8 kg, no congenital anomalies, not requiring mechanical ventilation at the time of the study, and ability to tolerate at least 150 mL/kg per day of feedings by 21 days of age. The study protocol was approved by the ethics committee of Chedoke-McMaster Hospital and was described to the parents, and signed consent was obtained. One group received only PTM and the second group received 50% PTM and 50% standard infant formula (PTM + F group) (Wyeth Ltd, Windsor, Ontario). Infants were assigned to one of two study groups depending on the ability of maternal lactation to support the needs of her infant(s). Most infants (balance 1, 5 of 6; balance 2, 3 of 5) in the PTM + F group were twins. Maternal milk production would have supported 1 infant but not 2. After the infants had been receiving full oral feeds for at least 1 week and were gaining greater than 10 g/kg per day, two 72-hour balance periods were carried out (Table 1).

Collection of Samples

Preterm milk samples were obtained from each infant's mother and were either fed fresh within 48 hours of pumping or frozen at -20°C until used. Each infant received only milk from his or her mother. During the balance study, 24-hour collections of milk were pooled, warmed to 37°C , and gently mixed. Individual feedings of formula and milk samples were measured into syringes by research staff. Formula or milk was bolus fed every 2 hours by nasogastric gavage. Urine and fecal samples were collected as previously described.⁹ Urine samples were collected using an acid-washed apparatus (made from fingers of plastic gloves and respiratory tubing) and drained into plastic containers that were subsequently refrigerated. Feces were collected in urine bags (U-bag, Hollister Ltd,

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Willowdale, Ontario). Plastic-backed ashless filter papers were placed beneath the head and posterior of the infant to collect any nitrogen losses due to regurgitation or urine leaks. All samples were stored at -20°C after collection. Stool samples were homogenized and freeze-dried prior to analysis.

Analyses

Milk, formula, urine, and stool samples were analyzed for total nitrogen, soluble nitrogen, and NPN by automated micro-Kjeldahl analysis (Tecator, Uppsala, Sweden).²⁵ The soluble fractions of PTM, formula, and rehydrated stool samples were isolated by ultracentrifugation at 189 000g for 1 hour at 4°C (Sorvall Model OT065B, Rotor AH650, Newton, Conn). Nonprotein nitrogen was determined in the soluble fractions of milk, formula, urine, and rehydrated stool samples following precipitation of proteins by the addition of an equal volume of 24% trichloroacetic acid and centrifugation at 10 000g. Urea nitrogen was determined using a modified urease-Berthelot reaction²⁶ (Sigma, St Louis, Mo). Human milk whey proteins were quantitated in the soluble fractions of PTM, urine, and fecal samples using rocket immunoelectrophoresis (lactoferrin, sIgA, serum albumin) and radial immunodiffusion (lysozyme, α -lactalbumin).²⁷ Immunoelectrophoresis was run in 0.025 mmol/L tricine buffer (pH 8.5) for 3 hours at 300 V.

To better characterize the soluble fecal fraction, crossed immunoelectrophoresis²⁷ of feces against anticolostrial whey and against antihuman serum was run on a subset of 10 infants from each dietary treatment. In this method, electrophoresis of the sample is run for 1 hour at 300 V in agarose without antibodies to separate the proteins by molecular weight. The plate is then rotated 90° and the sample electrophoresed for 3 hours at 300 V into agarose containing antibody. The location of specific proteins is determined by comparisons with plates run with purified proteins.

Proteins and peptides in soluble fecal extracts were separated by gel filtration Fast Protein Liquid Chromatography (Pharmacia Fine Chemicals, Piscataway, NJ). A sample volume of 50 μL was applied to a gel filtration column (Superose 12, Pharmacia Fine Chemicals) and eluted in 20 mmol/L ethanolamine buffer (pH 9.5) at a flow rate of 1.0 mL/min. The eluant was collected in 1-mL fractions and monitored at 280 nm.

Calculation of Results

Apparent nitrogen digestibility was calculated by the following formula: nitrogen intake minus fecal nitrogen output. Apparent nitrogen nutrition was calculated as follows: nitrogen intake minus fecal nitrogen output minus urinary nitrogen output. No adjustments were made for insensible nitrogen losses that consist mainly of cutaneous

losses.²⁸ Statistical analysis was carried out using a two-way analysis of variance, with study weight and study age as covariants.²⁹ Multiple mean comparisons were made using Duncan's Multiple Range Test and Bonferroni adjusted significance level. A value of $P < .05$ was chosen as the level of significance for both Duncan's and Bonferroni analyses. All statistical analyses were done with the Statistical Analysis System (SAS Institute, Cary, NC).

RESULTS

Infant Population

Twenty-four infants were recruited for the study. During the first balance, 18 infants received solely PTM and 6 received PTM + F. During the second balance, 9 of the original 18 PTM-fed infants received PTM again, 1 infant was switched to the PTM + F group, and 8 did not complete a second balance period.

PTM and Formula Composition

Mean nitrogen and protein concentration of PTM and formula used in this

study are presented in Table 2. Lactational day was calculated from the first day following parturition. Mean lactational day represents the mean value for the three 24-hour pooled PTM samples fed during the study period. There were no significant differences in the total nitrogen, soluble nitrogen, NPN, or urea nitrogen between PTM and the formula used. In human milk and formula samples, NPN was $19\% \pm 0.1\%$ of the total nitrogen, with urea nitrogen comprising 26% of the NPN (Table 2).

Nitrogen Intake

The distribution of nitrogen intake between the two dietary groups is shown in Fig 1. For PTM-fed infants $60\% \pm 2\%$ of the nitrogen intake was associated with human whey proteins, $20\% \pm 5\%$ with human casein, $20\% \pm 3\%$ with NPN. For infants receiving PTM + F, formula protein (bovine whey and casein) provided $41\% \pm 1\%$ of the nitrogen; human milk whey proteins, $30\% \pm 5\%$; human milk casein, $9\% \pm 2\%$;

Table 1.—Characteristics of Study Infants*

	PTM Group		PTM + Formula Group	
	Balance 1 (n = 18)	Balance 2 (n = 9)	Balance 1 (n = 6)	Balance 2 (n = 5)
Gestational age, wk	30.6 ± 1.8	30.7 ± 1.8	30.7 ± 1.9	30.6 ± 1.7
Birth-weight, kg	1.34 ± 0.23	1.30 ± 0.24	1.40 ± 0.27	1.40 ± 0.25
Study postnatal age, wk	2.9 ± 0.56	4.7 ± 1.2	3.1 ± 0.40	6.2 ± 2.2
Weight at time of study, kg	1.43 ± 0.28	1.50 ± 0.28	1.54 ± 0.23	1.72 ± 0.23
Milk volume, mL/kg per d	152 ± 30	165 ± 25	166 ± 15	144 ± 34

*Values represent mean \pm SD; PTM indicates preterm milk.

Table 2.—Nitrogen and Whey Protein Composition of Preterm Milk (PTM) and Formula*

Variable†	PTM		Formula† (n = 13)
	Balance 1 (n = 30)	Balance 2 (n = 21)	
Total N	3.03 ± 0.97	2.44 ± 0.26	2.72 ± 0.48
Soluble N	2.47 ± 0.29	2.00 ± 0.46	1.10 ± 0.32
NPN	0.50 ± 0.16	0.51 ± 0.19	0.56 ± 0.15
Urea N	0.13 ± 0.03	0.13 ± 0.03	0.14 ± 0.04
Protein§, g/dL	1.61 ± 0.51	1.21 ± 0.05	1.38 ± 0.21
α -Lactalbumin	2.70 ± 0.46	2.83 ± 0.63	...
Lactoferrin	3.60 ± 0.98	3.09 ± 1.11	...
Lysozyme	0.15 ± 0.05	0.19 ± 0.02	...
Serum albumin	0.62 ± 0.38	0.57 ± 0.33	...
Secretory IgA	2.56 ± 2.20	3.00 ± 2.35	...

*Values represent mean \pm SD milligrams per milliliter unless otherwise specified.

†SMA, Wyeth Laboratories, Windsor, Ontario.

‡N indicates nitrogen; NPN, nonprotein nitrogen.

§(Total N - NPN) \times 6.38.

and total NPN from formula and human milk, $21\% \pm 3\%$.

Nitrogen Balance

All infants were maintained in positive nitrogen balance (Table 3). Nitrogen intake, absorption, and retention were not significantly different between groups, with an average 85% digestibility and 71% retention. Nitrogen intake was highly correlated with nitrogen retention (milligrams per kilogram per day) in PTM-fed infants ($y = 86 + 1.1x$, $r = .98$, $P < .01$) and PTM + F-fed infants ($y = 211 + 0.74x$, $r = .97$, $P < .01$). Adjustment of nitrogen retention data by 11 mg/kg per day (previously estimated cutaneous losses²⁸) does not significantly decrease the retained nitrogen relative to intrauterine accretion rates.

Results for NPN and urea nitrogen intake and excretion are shown in Table 4. There were no significant differences in NPN or urea nitrogen intake between the groups. Urinary nitrogen and NPN were both decreased from balance period 1 to balance period 2 ($P < .05$). Balances for NPN and urea nitrogen were not calculated since it is impossible to determine whether the excreted NPN or urea nitrogen arose from the diet or as a product of protein metabolism.

Whey Protein Intake and Excretion

Intake and excretion data for the human milk whey proteins are presented in Table 5. Immunologically intact α -lactalbumin was not detected in feces of any infant. Due to the large degree of interinfant variability, no significant differences in the amounts of whey protein excretion were observed between the groups. Serum albumin was detected in the feces of 38% of the infants and accounted for 0.5% and 0.6% of the intake in PTM and PTM + F groups, respectively. Although total lactoferrin and lysozyme excretion were not significantly different between the two groups, when excretion is expressed as percentage of intake, the PTM + F group excreted a significantly greater proportion of lactoferrin (13% vs 5%) and lysozyme (18% vs 3%) than infants fed PTM alone.

Fecal Nitrogen Excretion

The different components of the fecal nitrogen are shown in Fig 2. Insoluble

nitrogen excretion was significantly greater in the PTM + F group. Excretion of nitrogen associated with soluble proteins was not significantly different between the two dietary groups. The insoluble fraction contains particulate matter, including sloughed intestinal and microbial cells. Nonurea NPN excretion was not significantly different between the two groups, but slightly less nitrogen was associated with fecal urea in the PTM + F-fed infants (14% vs 20%). The quantifiable components of

the fecal soluble protein fraction are shown in Fig 3. Fecal soluble nitrogen (total soluble nitrogen minus NPN) included several whey proteins—lactoferrin, sIgA, lysozyme, and serum albumin as well as other soluble proteins. Lactoferrin and sIgA together accounted for an average of 52% and 72% of the soluble proteins in feces of PTM-fed and PTM + F-fed infants, respectively.

Using crossed immunoelectrophoresis, four whey proteins were detected in the feces of all 10 infants studied, corre-

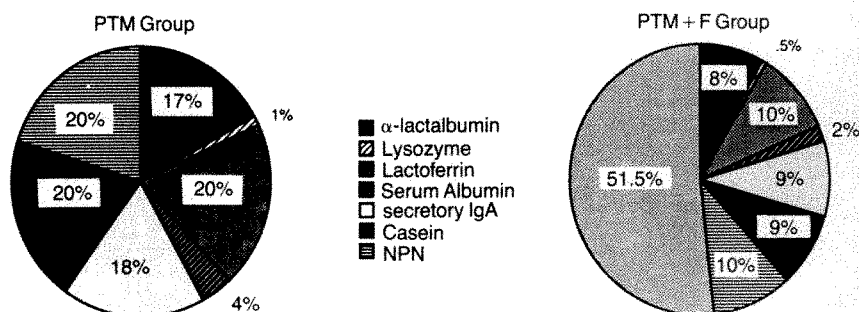


Fig 1.—Distribution of nitrogen intake as a percentage of total nitrogen in preterm milk (PTM)-fed and PTM and formula (PTM + F)-fed infants. In PTM + F-fed infants nonurea nonprotein nitrogen (NPN) and urea from milk plus formula are combined in NPN fraction.

Table 3.—Total Nitrogen Balance Data*

	PTM Group		PTM + Formula Group	
	Balance 1	Balance 2	Balance 1	Balance 2
Nitrogen intake	494 ± 171	410 ± 104	445 ± 123	366 ± 63
Nitrogen excretion				
Fecal	69 ± 29	55 ± 19	64 ± 10	66 ± 27
Urinary†	71 ± 22 ^a	54 ± 20 ^{ab}	69 ± 16 ^a	48 ± 9 ^a
Nitrogen absorbed, (%)	425 ± 171 (86)	352 ± 106 (86)	389 ± 110 (87)	297 ± 65 (81)
Nitrogen retained, (%)	358 ± 163 (72)	296 ± 104 (72)	322 ± 110 (72)	250 ± 70 (68)

*Values represent mean ± SD milligrams per kilogram per day; PTM indicates preterm milk. Values in parentheses indicate percentage on intake.

†Different superscript letters in this row denote significantly different values ($P < .05$).

Table 4.—Nonprotein Nitrogen (NPN) and Urea Nitrogen (N) Intake and Excretion*

	PTM Group		PTM + Formula Group	
	Balance 1	Balance 2	Balance 1	Balance 2
NPN intake	78 ± 28	88 ± 31	89 ± 36	70 ± 30
NPN excretion				
Fecal	36 ± 20	26 ± 12	20 ± 14	33 ± 16
Urinary†	65 ± 21 ^a	49 ± 17 ^{ab}	66 ± 15 ^a	38 ± 6.6 ^b
Urea N intake	20 ± 6	20 ± 6	26 ± 6.7	21 ± 3.0
Urea N excretion				
Fecal	15 ± 14	12 ± 15	9 ± 5	13 ± 8
Urinary	35 ± 22	46 ± 20	29 ± 16	17 ± 8

*Values represent mean ± SD milligrams per kilogram per day; PTM indicates preterm milk.

†Different superscript letters in this row denote significantly different values ($P < .05$).

sponding to lactoferrin, serum albumin, α_1 -antitrypsin, and sIgA (Fig 4). Three to four proteins were detected in the feces using the antibody against human serum proteins. Two were identified as α_1 -antitrypsin and serum albumin. A third high-molecular-weight serum protein was detected, possibly IgG. No other immunologically intact whey or serum proteins were detected by this method. Gel filtration chromatography of the soluble fecal extract using Superose 12 Fast Protein Liquid Chromatography revealed significant amounts of intact lactoferrin and sIgA in both PTM-fed and PTM + F-fed infants (Fig 5). In addition, large amounts of peptides whose molecular weights were less than 10 000 d were found in the feces of both groups of infants. The inset in Fig 5 shows the chromatographic separation of PTM on Superose 12 for comparison to the fecal extracts.

COMMENT

When comparing infants fed human milk with those receiving infant formula, one must consider the differences in nitrogen composition between bovine and human milk. Human milk consists of predominantly whey proteins,¹¹ several of which appear to be resistant to digestion within the gastrointestinal tract of both term¹⁷ and premature infants.¹⁹ In addition, 25% of the nitrogen in human milk is found as NPN.²¹ Partial utilization of NPN by the human infant has been demonstrated as retention of labeled urea nitrogen.^{22,30-32} Thus, while a proportion of the immune protein-bound amino acids in human milk may not be physiologically available to the infant for protein synthesis,¹² it is likely that some nitrogen from small-molecular-weight compounds may be retained by the infant.

In this study the effect of feeding solely PTM or a combination feeding of 50% PTM and 50% standard infant formula (PTM + F) on the intake and excretion of various nitrogen components was examined. There were no significant differences in overall nitrogen intake and excretion between the infants fed PTM or PTM + F. Nitrogen absorption from both diets was similar to that previously reported for premature infants fed mature human milk or standard infant formula.³³⁻³⁵ The goal for nitrogen accretion for premature infants is often set at levels that will allow growth and accretion

rates similar to those occurring in utero. Between 18 and 40 weeks of gestation, the nitrogen concentration in the fetus

rises linearly.³⁶ Based on these data and fetal body weights,³⁷ Jackson et al³⁸ calculated the nitrogen content of fetuses

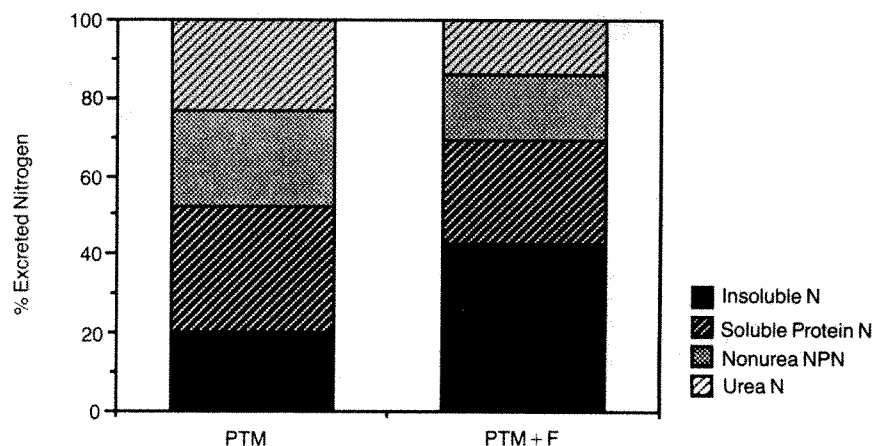


Fig 2.—Composition of fecal nitrogen excretion in preterm milk (PTM)- and PTM and formula (PTM + F)-fed infants. Results are expressed as a percentage of total nitrogen excretion. NPN indicates nonprotein nitrogen.

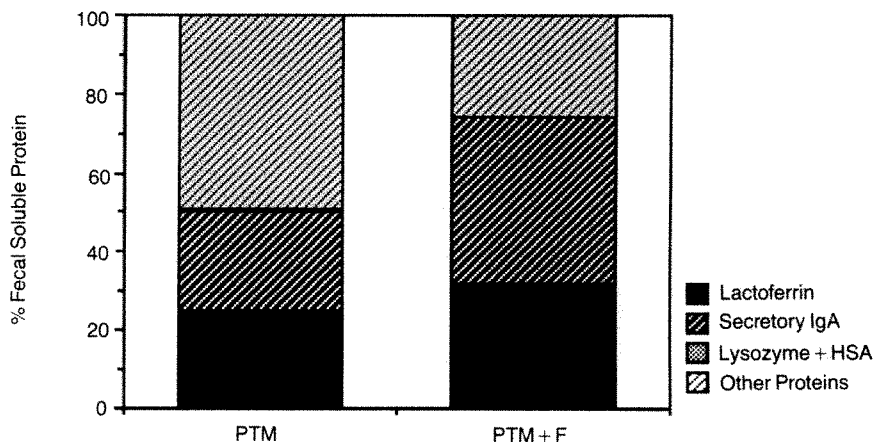


Fig 3.—Components of the fecal soluble protein (soluble nitrogen minus nonprotein nitrogen [NPN]) fraction of infants receiving preterm milk (PTM) or PTM and formula (PTM + F). HSA indicates human serum albumin.

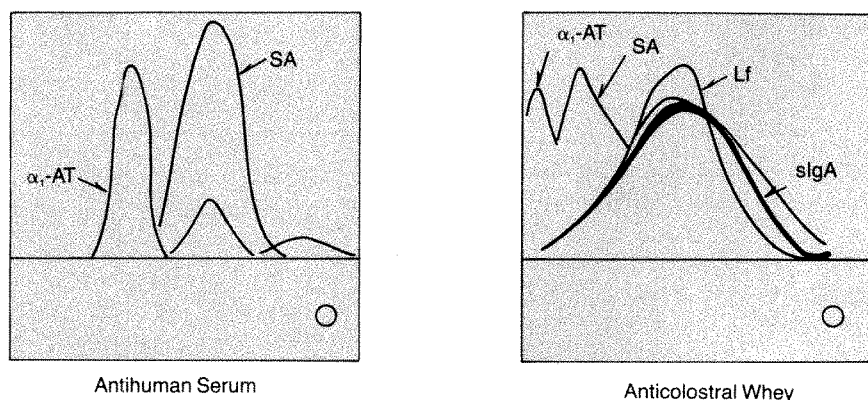


Fig 4.—Crossed immunoelectrophoresis of fecal extracts in gels containing antiserum and anticolostal whey. Peaks were identified as secretory IgA (sIgA), lactoferrin (Lf), serum albumin (SA), and α_1 -antitrypsin (α_1 -AT) by using purified proteins as standards.

growing along the 10th, 50th, and 90th percentiles. A comparison between the mean nitrogen accretion for our study infants and fetuses of similar postconceptual age growing at the 50th percentile is shown in Table 6. During balance period 1, all infants retained nitrogen at or above the 50th percentile for infants in utero. However, during balance period 2, nitrogen accretion for the PTM + F-fed infants dropped off to a rate similar to infants at the 10th percentile. Although the mean nitrogen retention was not statistically different between groups, the balance period 2 infants in the PTM + F group had the lowest mean total nitrogen intake (per kilogram of birth weight) and a 5% increase in mean fecal nitrogen excretion over the other groups. These differences may account for the lower nitrogen accretion in these infants.

There were no significant differences in intake of NPN or intake and excretion of urea nitrogen between the dietary groups, which reflects the similar nitrogen distribution in the PTM and infant formula (Table 2). This infant formula is based on electrodialyzed whey, which contains a relatively high proportion of NPN.³⁸ The significantly lower urinary NPN excretion in the PTM + F-fed infants in balance period 2 reflected the lower urinary total nitrogen excretion in this group and was associated with the lower nitrogen intake (per kilogram of birth weight). Although calculating NPN or urea nitrogen "balance" will not reveal anything about the true metabolic fate of the ingested NPN or urea nitrogen since these compounds are endogenously produced during protein catabolism, it is interesting to note that for balance 2, PTM-fed infants averaged a "positive" NPN retention.

Previous studies utilizing urea labeled with ¹⁵N (¹⁵N-urea) as a marker of dietary urea have demonstrated that animals^{39,40} and humans^{22,41} maintained on either low-protein diets or purified essential amino acids will utilize supplementary urea nitrogen. Several investigators^{22,30,32,42} have studied the bioavailability of dietary urea in both term^{22,30,32} and premature⁴² infants. The retention of ¹⁵N-urea ranged from 13% to 43% of the administered dose in these studies. There was no significant difference in retention between term infants fed formula³⁰ or human milk.³¹ However, pre-

mature infants⁴² and infants recovering from malnutrition²² or illness³² retained more of the administered ¹⁵N-urea than normal term infants.^{30,31} Rose and Dekker³⁹ demonstrated in the 1950s that the utilization of NPN as a source of nitrogen decreased when dietary protein was adequate. Therefore, the tendency for premature or compromised infants

to retain more urea nitrogen may be a reflection of their higher nitrogen requirements (per kilogram of birth weight).

Human milk whey proteins serve nutritional and functional roles for the infant. Secretory IgA, lactoferrin, and lysozyme have been postulated to contribute to the human milk-fed in-

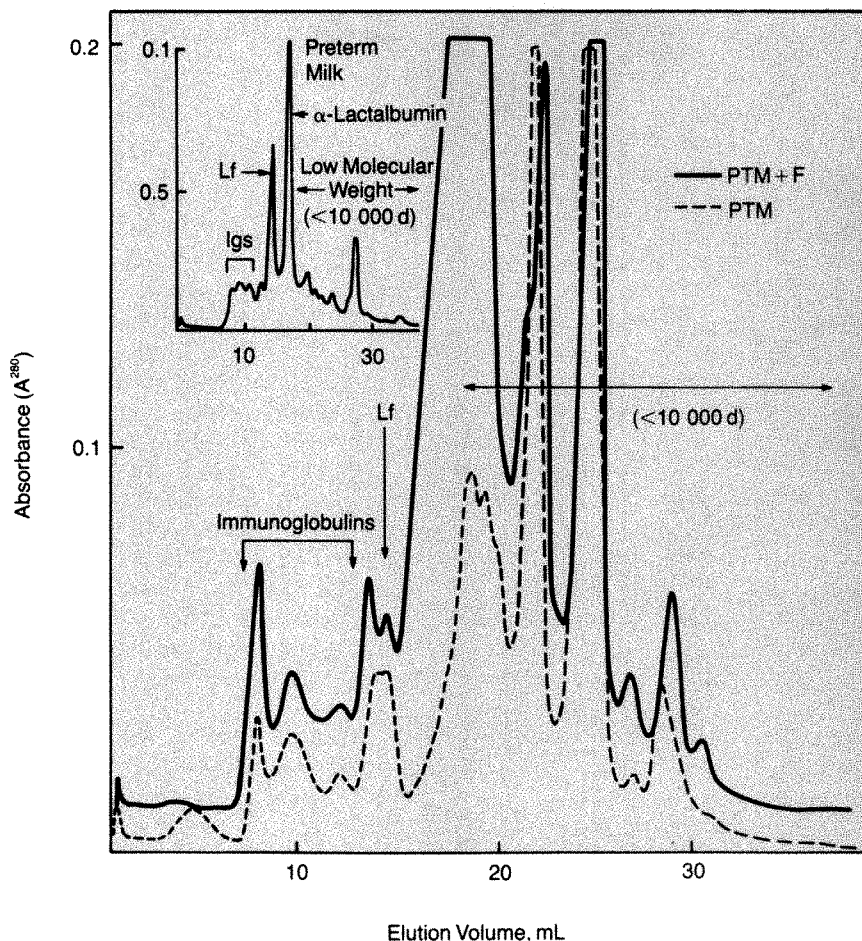


Fig 5.—Superose 12 Fast Protein Liquid Chromatography separation of the soluble fecal extracts from infants receiving preterm milk (PTM) and PTM and formula (PTM + F). Inset shows chromatographic separation of preterm human milk. Lf indicates lactoferrin.

Table 5.—Intake and Fecal Excretion of Human Whey Proteins*

	PTM Group (n = 23)		PTM + Formula Group (n = 10)	
	Intake	Excretion (%†)	Intake	Excretion (%†)
α-Lactalbumin	425 ± 104	0 (0)	171 ± 32 ^a	0 (0)
Serum albumin	102 ± 67	0.56 ± 0.13 (0.5)	57.21	0.34 ± 0.6 (0.6)
Lactoferrin‡	492 ± 217 ^a	24 ± 26 (5)	262 ± 80 ^a	33 ± 22 (13 ^b)
Lysozyme‡	34 ± 10 ^a	1.1 ± 1.2 (3 ^a)	11 ± 8 ^b	2.0 ± 1.5 (18 ^b)
Secretory IgA‡	460 ± 383 ^a	110 ± 150 (24)	138 ± 83 ^a	38 ± 58 (27)

*Values represent mean ± SD milligrams per kilogram per day.

†Calculated as a percentage of intake.

‡For each protein different superscript letters denote significantly different values between groups ($P < .05$).

Table 6.—Comparison of Nitrogen (N) Retention of Study Infants With Calculated In Utero N Accumulation*

	Postconceptional Age at Study, wk	N Accretion, mg/kg per d		Actual Calculated Accretion, %
		Observed Retention	Calculated In Utero†	
PTM				
Balance 1	33.0 ± 2.1	358 ± 163	301	119
Balance 2	34.5 ± 2.2	296 ± 104	309	96
PTM + F				
Balance 1	33.7 ± 1.4	322 ± 110	304	106
Balance 2	36.2 ± 2.4	250 ± 70	319	78

*Values represent mean ± SD; PTM, preterm milk; and F, formula.

†From Jackson et al³⁸ for infants growing along the 50th percentile.

fant's resistance to gastrointestinal and respiratory tract infections.^{48,44} Although the persistence of lactoferrin, sIgA, and lysozyme through the gastrointestinal tract of the infant is well documented, and has been demonstrated in both term^{18,17,18} and premature^{19,20} infants, one of the aims of the present study was to better characterize the contribution of the whey proteins to overall nitrogen intake and fecal excretion. The contribution of human milk whey proteins to overall nitrogen intake reflects the composition of the infants' diet, constituting 60% of the nitrogen intake in PTM-fed infants and 30% in PTM + F-fed infants. We attempted to quantitate cow's milk whey protein intake and excretion using antibodies against bovine whey proteins. However, due to the extensive modification of the proteins during formula manufacturing, they were no longer recognizable by the antibodies.

The presence of intact lactoferrin and sIgA in fecal extracts from both PTM-fed and PTM + F-fed infants was demonstrated by gel filtration chromatography (Fig 5). In addition, a large amount of peptides with molecular weight greater than 10 000 d was observed in both sets of infants. Fecal proteins are generally quantitated by either immunoelectrophoresis^{17,19} or enzyme-linked immunosorbent assay²⁰; however, each of these assays measures only whether the protein is "immunologically" intact and not if it is structurally intact. When quantitating fecal lactoferrin by rocket immunoelectrophoresis, we observed "double rockets" in some samples. If lactoferrin were partially degraded, yet still intact enough to be recognized by the antibody, the smaller fragments would migrate farther than the intact molecule in the electrophoretic field, re-

sulting in two rockets. No double rockets were observed for milk lactoferrin, fecal or milk sIgA, or serum albumin. Recent investigations in our laboratory⁴⁶ have demonstrated that "half-lactoferrin," produced by proteolytic digestion at low pH, is immunologically reactive. In addition, the half-lactoferrin showed similar binding to its intestinal lactoferrin receptor as intact lactoferrin. Thus, even after partial digestion, ie, cleavage into two iron-binding fragments, lactoferrin retains enough structural integrity to interact with the receptor and potentially serve a functional role in vivo. Larger fragments of lactoferrin in the stool of preterm infants have been reported by Goldman et al.⁴⁶ However, in their study sodium dodecyl sulfate, a denaturing agent that dissociates all peptides from each other, was used, while we used gel filtration and nondissociating conditions. It has been shown that the two larger fragments of transferrin⁴⁷ and lactoferrin⁴⁸ self-associate. Therefore it is likely that lactoferrin in the stool is present both as large fragments and in intact form.

Whey proteins in the feces may arise from several sources: undigested milk proteins, endogenous synthesis and secretion into the intestinal lumen, or by leakage into the intestine from serum. Endogenous secretion of sIgA and lactoferrin in formula-fed term^{44,49} and premature²⁰ infants has been reported to be low. In term infants, no fecal sIgA was detected in formula-fed infants less than 3 weeks of age.⁴⁴ Spik et al⁴⁹ detected a constant value of 0.5 mg of lactoferrin every 24 hours in the feces of formula-fed term infants, probably representing endogenous synthesis. The infants in our study were excreting between 30 and 45 mg of lactoferrin every 24 hours,

which is well above this level. Premature infants receiving formula excreted only 0.5% to 3.0% of the levels of "protective" proteins as infants receiving fortified human milk.²⁰ These studies suggest that the role of endogenous secretion in contributing to fecal proteins is limited in the young term and premature infant. The presence of serum albumin and α_1 -antitrypsin in feces may arise from either ingested milk or leakage from serum. Crossed immunoelectrophoresis of fecal extracts against antiwhey protein and antiserum protein antibodies showed reactivity with both of these proteins. Other soluble fecal proteins may include minor whey proteins, other serum proteins, or proteins arising from the infant's gut or intestinal flora. In the premature infant, leakage of such proteins into the gut may play a larger role than in the term infant due to his or her immature gut development.

Although the levels of intake of serum albumin, lactoferrin, and lysozyme were higher in the PTM-fed group, total excretion (milligrams per kilogram per day) of the proteins was very similar between the groups, which seems to reflect steady-state excretion. In contrast, mean levels of sIgA excretion (milligrams per kilogram per day) were 3.0-fold higher in the PTM-fed group than the PTM + F group, which may reflect the 3.3-fold higher intake of sIgA. Therefore, for sIgA the level of excretion may be mediated by intake, although this study and previous studies have failed to positively correlate intake and excretion.²⁰

Although metabolic balance studies tend to be biased toward overestimation of intake and underestimation of intake, when carried out carefully these errors can be limited. In addition, since the comparisons in this study were made between groups, error would be in the same direction. Therefore, in spite of their limitations, nitrogen balance studies provide a noninvasive, nonisotopic method for assessing nitrogen utilization from different diets.

In this study it was demonstrated that premature infants maintained on their own mother's milk attain nitrogen balance with nitrogen accretion rates similar to those of the reference fetus growing at the 50th percentile for the first 5 weeks postnatally. If we assume

that all of the fecal whey proteins are arising from persistence of milk proteins through the gastrointestinal tract, this represents a loss of up to 33% (PTM-fed) to 59% (PTM + F-fed) of the ingested protein and thus amino acids for protein synthesis. However, it must be cautioned that, as with NPN, without the use of labeled milk protein it is impossible to distinguish between fecal proteins that are of milk origin from those endogenously produced; therefore, these percentages may represent an overestimation. Although it was not studied in these infants, studies with other premature infants in the neonatal unit of Chedoke-McMaster Hospital showed that approximately 25% of ^{15}N -urea supplemented to human milk is retained by the infant.⁴² This level of retention may represent up to 5% of the infant's nitrogen needs. The potential loss of whey proteins via fecal excretion and the speculation that at least part of the NPN can be utilized by the infant for protein synthesis underscores the difficulty in determining what represents the "true" utilizable protein or nitrogen content of human milk.

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Cardiac Malformations in Relatives of Infants With Hypoplastic Left-Heart Syndrome

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• In a pilot study of relatives of infants with hypoplastic left-heart syndrome (HLHS), we obtained a medical history, cardiovascular examination, and echocardiogram in 48 first-degree relatives of 11 probands with isolated HLHS and 3 with HLHS and noncardiac malformations. Echocardiography confirmed heart defects in 5 of 41 relatives of patients with isolated HLHS. In four instances, the cardiac abnormality was unrecognized. Among 7 relatives of infants with HLHS and extracardiac anomalies, no heart defects were detected. Cardiac defects occurred in first-degree relatives of probands at a frequency higher than previously predicted by an additive multifactorial model of inheritance. These findings suggest that first-degree relatives of HLHS probands may have an increased risk for subclinical cardiac defects and that genetic factors likely contribute to the cause of left-heart blood-flow lesions.

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Although hypoplastic left-heart syndrome (HLHS) accounts for only a small proportion of clinically recognized congenital cardiovascular malformations,^{1,2} it remains one of the most severe types of malformation, with an untreated mortality of 100% and an uncertain surgical future.^{3,4} Determining the cause of HLHS is important because of the major medical-surgical, psychological, and economic issues created by caring for the family faced with a newborn with HLHS. Recurrence-

risk counseling has been based on the assumption that HLHS has a multifactorial origin. Thus, a recurrence risk of 3%, the square root of the population frequency as predicted by the multifactorial model,⁵ has often been cited in the past.⁶

Recent data from a population-based study of congenital cardiovascular malformations in liveborn infants challenged this interpretation.⁷ We found that the recurrence risk, ie, the risk of a heart defect to relatives born before the study infant, was higher than predicted by the multifactorial model. For isolated HLHS, eg, the reported recurrence risk approached 13%. A similar pattern of increased recurrence risk had also been noted in recent clinical studies of parents with left-heart defects, where 12% to 26% of infants born to mothers or fathers with aortic stenosis were found to have congenital cardiovascular malformations, usually of a similar type.^{8,9} Concordance data from these studies, from a population referred for fetal echocardiography because of a prior infant with left-heart disease,¹⁰ and from experimental models reviewed by Clark,¹¹ suggest that left ventricular outflow tract defects, ranging from bicuspid aortic valve (BAV) to HLHS, may be developmentally related. Left-heart defects reported in affected relatives of infant patients led us to initiate a pilot study to document the existence and nature of congenital cardiovascular malformations and to investigate the possibility that the incidence of previously unrecognized structural cardiac defects might be higher than predicted by the multifactorial model in the relatives of infants with HLHS.

PATIENTS AND METHODS

Families for this pilot project were drawn from the Baltimore-Washington Infant Study, a population-based case-control study of congenital cardiovascular malforma-

tions in the State of Maryland, the District of Columbia, and five counties in Northern Virginia.¹ For our purposes, the diagnostic group with HLHS included only infants with aortic atresia and mitral stenosis-atresia with hypoplasia of the left ventricle. Diagnosis was confirmed by echocardiography, angiography, surgery, autopsy, or a combination of these.

Fourteen families in the Baltimore-Washington Infant Study who had at least one infant affected with HLHS registered with Pediatric Cardiology at the University of Maryland Medical System or The Johns Hopkins Hospital, Baltimore, Md, agreed to participate. First-degree family members were examined by one of us, a senior cardiologist (J.I.B. or E.B.C.). Blood pressure in the upper and lower extremities was taken manually, automatically, or by a combination of blood pressure devices with use of the appropriate cuff for age and size of the subject. Clinical cardiopulmonary examination was performed with special attention to the presence of pathologic murmurs, systolic clicks, and aortic-arch obstruction.

Echocardiography was performed under the direct supervision of a study center physician with the assistance of a skilled pediatric echocardiography technician. Standard M-mode measurements of left ventricular diastolic and systolic dimension; mitral valve excursion, and aortic and left atrial size were obtained. Real-time echocardiographic evaluation included detailed study of mitral valve motion and papillary muscle orientation. Real-time guided Doppler determination of mitral valve inflow and left ventricular outflow was also performed.

All echocardiographic tapes were evaluated by a second cardiologist who had not seen the family and was unaware of the physical examination results. The diagnosis of a heart defect was confirmed only when both cardiologists agreed on the presence of the defect as demonstrated by echocardiography and supported by physical examination. At the time of examination, a medical history and detailed pedigree were obtained from the parents.

This protocol was approved by the Human Subjects Review Committee at each institution. Each family provided informed consent before participation.

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Extracardiac Anomalies in Patients With Hypoplastic Left-Heart Syndrome			
Patient	Extracardiac Anomalies	Karotype	Sex
3	Absent left kidney; right hydronephrosis	Not obtained	F
7	Single umbilical artery; horseshoe kidney; skeletal abnormality	Not obtained	F
8	Optic nerve hypoplasia; cataract	46,XY	M

RESULTS

Of 33 local families with an infant diagnosed with HLHS, 14 were available and agreed to participate in the study. Of the remaining families, 2 families had moved out of state, 2 identified through searches of autopsy records were unwilling to become involved, and the other families declined the clinical testing procedures. No discernible differences were noted in patient diagnosis, family size, or demographics between participating and nonparticipating families.

Forty-eight first-degree relatives from 14 families were available for examination. Three fathers did not participate in the studies, and thus their cardiac status is unknown. In addition, one 14-month-old sibling had normal cardiopulmonary examination results but was too uncooperative for detailed echocardiographic evaluation.

All 14 infant patients were dead when their families were examined. Three of these infants had additional extracardiac anomalies, as shown in the Table. These 3 included 2 females with renal defects, 1 of whom had, in addition, a skeletal abnormality that was thought to be an autosomal dominant form of ectrodactyly, based on the family history (parent and second-degree relative). Cytogenetic analysis was not performed on either of these infants. The male infant was born with optic-nerve hypoplasia and a unilateral cataract of unknown cause. Autopsy findings were noncontributory, and he had a normal karyotype. No heart disease was noted in any first-degree relative.

Eleven infants had no recognized phenotypic abnormalities apart from their HLHS. In this group, echocardiographically normal relatives were found in 7 of the families. Among the 4 families in which abnormal echocardiographic findings were identified (Fig 1), none of the parents had reported or suspected that they had a heart defect when ini-

tially interviewed for the Baltimore-Washington Infant Study.

By clinical and echocardiographic examination, four parents were found to have a BAV. In 2 families, a single parent with BAV was noted, while in 1 family, both parents had BAV. One sibling with BAV and mild aortic stenosis had been identified before his sister was born with HLHS. The excessive pregnancy loss in this family was attributed to an incompetent cervix. Thus, among the families with isolated cases of HLHS, 5 (12.2%) of 41 of the examined relatives had a cardiac abnormality suspected by physical examination and confirmed by echocardiography; all defects involved the left ventricular outflow tract.

COMMENT

Aggregation of left-heart defects became evident to us from data analyzed in the Baltimore-Washington Infant Study.⁷ When isolated anatomic heart defects were grouped by presumed developmental mechanism, such as altered blood flow through the embryonic heart, the contrast was striking between the frequency of affected relatives—particularly siblings—of probands with left-heart defects compared with the relatives of probands with all other types of cardiac malformations (Fig 2). Moreover, there was a high degree of concordance of reported lesions in families. Evidence that a spectrum of left-heart defects may result from a single mechanism is also suggested by analysis of human heart specimens and the hearts of experimental animals.^{11,12} The phenotypic expression may range from mild defects, such as BAV, to the most clinically severe manifestation, HLHS.

Isolated congenital cardiovascular malformations have traditionally been thought to be multifactorial disorders, resulting from the small additive effects of several genes and from environmen-

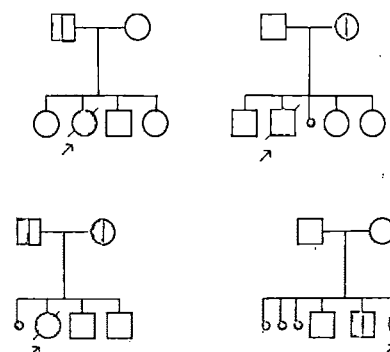


Fig 1.—Pedigree of four families of proband (arrow) with hypoplastic left-heart syndrome and additional affected family members. Large solid symbols indicate patients with hypoplastic left-heart syndrome; partially shaded symbols, individuals with bicuspid aortic valve; small solid circles, abortuses; squares, males; circles, females; and slashes, dead.

tal factors.⁶ Recurrence risk is, therefore, usually lower than in mendelian disorders, and recurrence is modified for each family by the number of affected relatives and the severity of defect in the proband. In the report from the Baltimore-Washington Infant Study, the multifactorial expectation of recurrence of 1% to 5% was observed in mothers and fathers of infants with left-heart defects, and in mothers, fathers, and siblings of infants with all other types of congenital cardiovascular malformations. However, among sibling probands with left-heart defects, the reported frequency substantially exceeded the frequency expected under a multifactorial mode. Moreover, the affected relatives of infants with left-heart defects, though concordant with the developmental group, were not always concordant for a specific anatomic lesion. These findings led us to investigate a subset of available families in more detail.

Twelve percent of the examined relatives of a subset of infants with isolated HLHS had BAV, compared with a population estimate for BAV of 0.9% to 1.3%.¹³ Bicuspid aortic valve may be considered a subclinical left-heart blood-flow defect. This suggests that minor left-heart defects, compatible with essentially normal life and of undetected, may occur more frequently among relatives of infants with HLHS than in the general population.

Several possible explanations may account, at least in part, for the finding of higher rates of left-heart lesions in

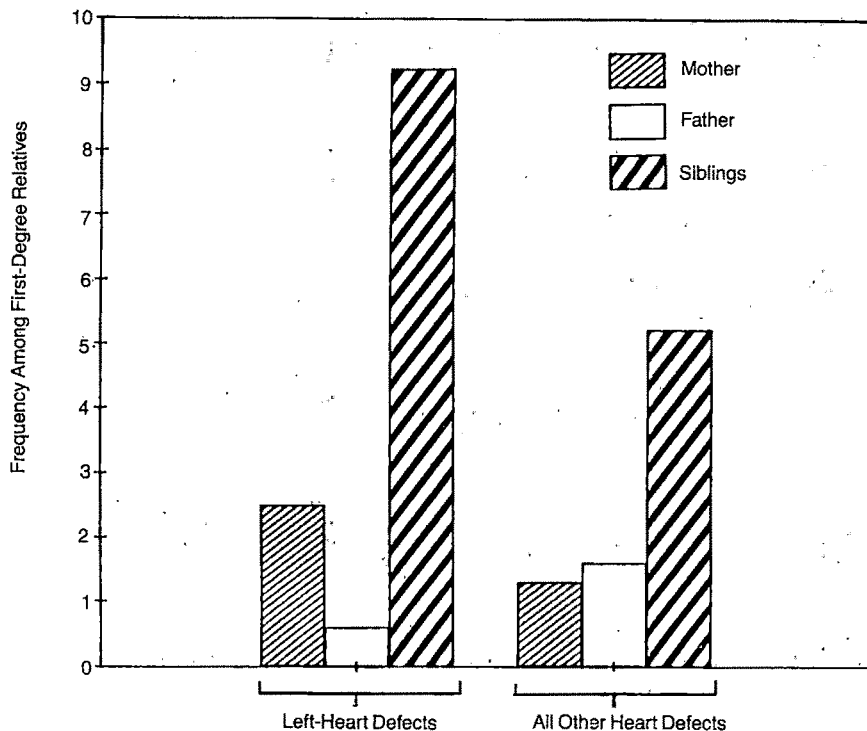


Fig 2.—Percentages of cardiac malformations among first-degree relatives of infants with congenital heart disease, from the Baltimore-Washington Infant Study.⁷

study families. First, the increase over population frequency may be a chance occurrence in this preliminary study. Second, mild forms of the spectrum of left-heart malformations in families of infants with HLHS may reflect risks appropriate to a multifactorial threshold trait with identification through severely affected probands, thus accounting for the high frequency of affected relatives. According to the Carter hypothesis,¹⁴ severely affected probands would have higher frequencies of affected first-degree relatives than more mildly affected patients. More data from relatives of patients representing the spectrum of left outflow defects would be necessary to confirm this hypothesis.

A third alternative is that, in at least some of the families, left-heart defects may be under the control of a major gene or genes with variable expression and identification limited by selection against infants with HLHS, since these individuals do not reproduce. Under this hypothesis, families in which the gene(s) was segregating would have higher proportions (up to 50% if single-gene dominant) of individuals with the "affected" genotype. Expression of that genotype could then depend on addi-

tional genetic or environmental modifiers, so that some individuals with the genetic predisposition could have milder expression, ie, BAV. All genotypes surviving the newborn period, by definition, would have milder lesions than HLHS.

This pilot study cannot prove any of these hypotheses, especially with the potential for heterogeneity. Formal genetic-model testing requires larger sample sizes, and further studies are necessary to calculate accurate risks for genetic counseling to be established.

In the short term, clinical management can be altered by offering fetal echocardiography to evaluate subsequent pregnancies in families in which serious left-heart defects have occurred. Echocardiography of first-degree relatives of infants with HLHS and other severe left-heart malformations can also be considered in these families to identify the presence of subclinical defects such as BAV, which would modify recurrence counseling even if the multifactorial model were used. The use of antibiotic prophylaxis and periodic monitoring by a cardiologist should also be considered.

In an era when surgical palliation of HLHS or cardiac transplantation is be-

ginning to hold promise for infants, allowing growth and maturation, it becomes even more urgent to investigate potential genetic influences in congenital cardiovascular malformations. When continued improvement in surgical technique and medical control of rejection allow survival of infants with HLHS into their reproductive years, the full influence of the severe end of the spectrum of left-heart flow lesions will be realized.

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GENERAL PEDIATRICIAN BC/BE — Southern California. Full-time general pediatrician to join busy multi-specialty group practice in north San Diego County. Competitive salary and fringe benefits. Send CV to: Physician Recruitment, The Mission Park Clinic, 2201 Mission Avenue, Oceanside, CA 92054. Or call: (619) 967-4892.

BC/BE — One or more pediatricians for a rapidly growing community outside of Atlanta. Excellent compensation and benefit package. Call or write Peter Avento, P.O. Box 617, Jensen Beach, 34958-0617; or (407) 334-1057.

Professional Opportunities

UTAH — Pediatrician to replace fourth pediatrician, who is retiring, in multi-specialty clinic. Shared call. Happy group. Guaranteed salary. University, mountain recreation, skiing. Contact: Neal J. Byington, 225 East 400 North, Logan, UT 84321. (801) 752-0422.

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PLEASE NOTE — Address replies to box number ads as follows: Box number, _____, c/o AJDC, P.O. Box 1510, Clearwater, FL 34617.

Professional Opportunities

MASSACHUSETTS — Pediatrician, BC/BE, needed to join two others in busy private practice one hour west of Boston. Good coverage, hospital and salary. Mail CV to: Felix Perriello, MD, 114 Water Street, Milford, MA 01757. (508) 473-0231.

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PEDIATRICIANS — Southeast United States: Several progressive groups seeking board-certified or board-eligible pediatricians. Send CV to: CPR Associates, P.O. Box 235005, Montgomery, AL 36123-5005.

ALABAMA/FLORIDA AREA — Looking for security? Want to be your own boss? BC/BE pediatrician needed for a 70-bed hospital position. \$90,000 salary plus benefits. Send CV to: HQS, 6053 Tammy Drive, Alexandria, VA 22310; or call: (800) 359-1666.

HOUSE BASED PEDIATRICIANS — Huntington Memorial Hospital in Pasadena, California, a University of Southern California affiliate, is seeking four board-eligible /-certified pediatricians to provide in-house coverage for its 34-bed pediatrics floor. The salary and comprehensive benefit package is competitive with HMOs or other salaried positions in southern California. Send CV and list of three references to: Edgardo L. Arcinue, MD, Head, Department of Pediatrics, 100 Congress Street, Pasadena, CA 91105. (818) 397-8688.

BABY YOUR CAREER — Southwest Medical Group, PA is currently seeking BC/BE pediatricians. Our large medical group, specializing in managed care, is a staff model office with 36 full-time providers. We offer an attractive compensation package and competitive salaries, plus the opportunity to work in one of our four locations in San Antonio. For more information call: (512) 558-1027. Or send your curriculum vitae to: Southwest Medical Group, PA, MedCentre Plaza, 8431 Fredericksburg Road, Suite 510, San Antonio, TX 78229. EOE M/F.

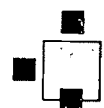
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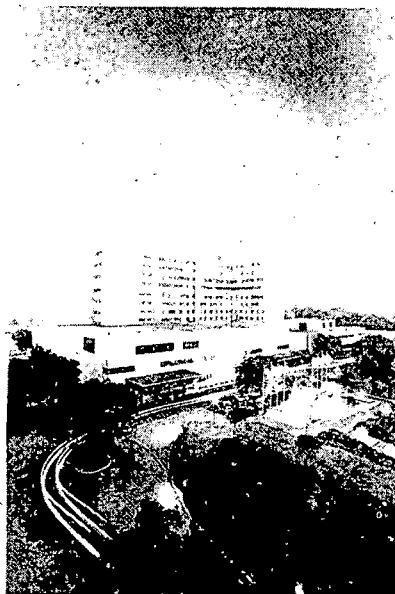
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Professional Opportunities

HERSHEY, PENNSYLVANIA — Rapidly growing solo practice with C.R.N.P. seeking two BC/BE pediatricians. Practice has special emphasis on behavioral developmental pediatrics, allergy/asthma. Two community hospitals with Level 3 nurseries available. Many life style amenities. Contact: Glen S. Bartlett, MD, Hershey Pediatric Center, 441 East Chocolate Avenue, Hershey, PA 17033. (717) 533-7850.

WESTERN STATES — BE/BC pediatricians for multi-specialty clinics, hospitals. Also, private California practices for sale. Call/send CV: Bradshaw Associates, 21 Altamont, Orinda, CA 94563. (415) 376-0762.

PEDIATRICIAN needed for rapid growth area. 119-bed, rural hospital located between Nashville, Tennessee and Huntsville, Alabama. Substantial monthly salary guarantee plus a quiet lifestyle in a beautiful country setting. Contact: Doug Dailey, Lewisburg Community Hospital, P.O. Box 1609, Lewisburg, TN 37091. (615) 359-6241.

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PEDIATRICIAN — Upstate New York. BC/BE to be fifth pediatrician in this growing specialty group of eleven physicians. Formal affiliation with tertiary center Rochester General Hospital. Demanding and exciting group practice of general pediatrics. Generous income and benefits package. Medical liability insurance covered. Lake and orchard area; great sailing, fishing, skiing. Write with CV to: Dr. Richard Endres, FAAP, Rochester General Wayne Medical Group, P.O. Box A,odus, NY 14551.

NEONATOLOGIST — Monmouth Medical Center, a 506-bed tertiary care referral center on the central New Jersey coast seeks an additional neonatologist for a 23-bed, Level III regional newborn care unit. There are over 3,700 in-house deliveries with active maternal and infant transport programs for the 10,000 annual deliveries in the region. Close collaboration with the perinatal program and pediatric subspecialties. The hospital is a major university teaching affiliate with faculty appointment and clinical research opportunities. CV to: Kirby Rekedal, MD, Director, Division of Neonatology, Monmouth Medical Center, Long Branch, NJ 07740. (201) 870-5175.

Professional Opportunities

PENNSYLVANIA — BC/BE pediatrician to join established practice. Start July 1990. Competitive salary and benefits, leading to partnership. Excellent opportunity, attractive area 35 miles west of Philadelphia (Chester County). Send CV to: Box #102, c/o AJDC.

LOMPOC, CALIFORNIA — BC/BE pediatrician. Immediate opening to join dynamic, large multi-specialty clinic at branch office in Lompoc. Competitive starting salary and full benefit package. Excellent living and practice environment. Send CV to: Barbara Volk, Santa Barbara Medical Foundation Clinic, P.O. Box 1200, Santa Barbara, CA 93102. EOE.

PEDIATRIC CRITICAL CARE PHYSICIAN needed to join three others in multi-disciplinary tertiary care facility providing intensive care to children from southwest Michigan. Opportunity for research and academics. Excellent salary and benefit package. Call collect or send CV to: Deb Hartman, Bronson Management Services, 210 East Vine Street, Kalamazoo, MI 49001. (616) 344-6444.

PRACTICE IN THE LAND OF PLEASANT LIVING — Multi-specialty group in southern Maryland is looking for the right BE/BC pediatrician to join one pediatrician, two family practitioners, two internists in primary care group in rapidly growing rural area, twenty miles southeast of Washington, DC. Salary and benefits package beyond compare. Contact Nancy Howell today, for more information: (301) 645-4528, or after 8:00 PM (301) 870-3944.

Faculty Positions

TEXAS — Faculty needed for the division of general pediatrics of a new hospital of The University of Texas Medical School-Houston. The hospital has 169 nursery and 54 pediatric beds, and anticipates 20,000 outpatient visits and 7,500 deliveries per year. Responsibilities will include teaching, patient care and research. Fellowship training and prior academic experience preferred. Hiring at all academic ranks. Contact: Dr. Will Risser, Department of Pediatrics, UT Medical School, P.O. Box 20708, Houston, TX 77225. (713) 794-5126. The University of Texas is an equal opportunity employer. Women and minorities are encouraged to apply.

NEONATOLOGIST needed for level II university-affiliated intensive care nursery in Philadelphia, Pennsylvania. Responsibilities include resident teaching, clinical duties and clinical research. Appointment to university faculty. Salary commensurate with experience. Contact: Mark Bateman, Executive Vice-President, Episcopal Hospital, Front Street and Lehigh Avenue, Philadelphia, PA 19125. (215) 427-7163.

SOUTHEAST USA — Academic pediatrician: Teach medical students and family practice residents. Direct patient care and clinical research interests required. Alabama state medical license required. Should be board-eligible or board-certified. The University of Alabama is an equal opportunity/affirmative action employer. Send inquiries with CV to: David C. Hefelfinger, MD, Department of Pediatrics, 700 University Boulevard East, Tuscaloosa, AL 35401. (205) 348-1304.

Fellowships

PEDIATRIC NEUROLOGY FELLOWSHIP position available July 1990. Involves development of individual research potential and training in basic clinical skills. Candidates with MD, PhD degrees, or those interested in an academic career in pediatric neurology are particularly encouraged to apply. Send CV to: Leon Epstein, MD, Unit Chief, Pediatric Neurology, Box 631, University Medical Center, 601 Elmwood Avenue, Rochester, NY 14642. U/R is an equal opportunity/affirmative action employer.

Practices Available

CALIFORNIA — Thriving quality solo pediatric practice for sale. Located in rapidly growing southern California inland valley close to hospitals with all subspecialties for consultation. Reply: Box #101, c/o AJDC.

PEDIATRIC CHRONIC DISEASE SPECIALIST

The Department of Pediatrics, University of New Mexico School of Medicine, is seeking a board-certified/-eligible pediatrician at the assistant/associate professor level (tenure-line) as Director of Chronic Diseases and Director of Pediatrics at Carrie Tingley Hospital, an integral component of Children's Hospital of New Mexico.

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References: 1. Tarlin L, et al: *Am J Dis Child* 1972;124:880-882. 2. Aspirin or paracetamol? *Lancet* 1981;ii:287-289. 3. Data on file, McNeil Consumer Products Company.

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